SYNTHESIS AND APPLICATION OF NEW LIGANDS DERIVED FROM *N*-HETEROCYCLIC CARBENES, PHOSPHINES AND PHOSPHITES FOR ASYMMETRIC HYDROGENATION

A Dissertation

by

SAKUNCHAI KHUMSUBDEE

Submitted to the Office of Graduate and Professional Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Chair of Committee,	Kevin Burgess
Committee Members,	Oleg V. Ozerov
	Jiong Yang
	Katy Kao
Head of Department,	David H. Russell

December 2013

Major Subject: Chemistry

ABSTRACT

N-Heterocyclic carbene and phosphorus ligands have been synthesized and used for many catalytic reactions including chiral analogs of Crabtree's catalyst for asymmetric hydrogenation. These catalysts have been studied extensively, especially on hydrogenation of "largely unfunctionalized" alkenes, for more than a decade. These substrates, however, could not be easily modified leading to limited applications for organic synthesis. As a result, asymmetric hydrogenations of substrates that have non-coordinating functional groups have gained more attention because the products are chirons that could be used to synthesize many natural products.

Even though many chiral analogs of Crabtree's catalysts have been studied, none of these catalysts is perfect. Different catalysts could be suitable for different substrates. This point motivated us to investigate asymmetric hydrogenation of different substrates using our *N,carbene* Crabtree's catalyst analog; for example, *α-methyl-γ-alkyl-γ-amino acid* derivatives can be obtained with high stereoselectivities. Moreover, the same point also inspired us to synthesize the new *N*-heterocyclic carbene ligands to compare the effect on different catalysts that have related structure.

Design new ligands to obtain effective catalysts, however, needs high experience and it is possible time consuming with unpredictable outcomes. Using the screening method with *mono*-chelating phosphorus ligands synthesized from cheap and easily obtained starting materials might be possible solution. However, we cannot rule out the possibility that *bi*-chelating ligand of the related structure might give better selectivities. Cross metathesis is an easy method that can link two parts together to convert *mono*-chelating ligand to *bi*-chelating one. Using metathesis combined with catalysis "*metacatalysis*" is one method to compare catalytic activity of *mono*- and *bi*-dentate ligands. However, the result indicated that most this method was suitable in some cases but not all.

DEDICATION

To

my parents, Saeree Khumsubdee and Yanimon Khumsubdee

ACKNOWLEDGMENTS

I would like to express the deepest appreciation to my advisor, Prof. Kevin Burgess, for all his support during my study. Dr. Burgess's passion for excellence and determination for success play a significant role in my academic career at Texas A&M University. This dissertation would not be possible without his guidance.

I would like to thank my committee members, Dr. Oleg V. Ozerov, Dr. Jiong Yang, and Dr. Katy Kao, for serving on my graduate advisory committee. I genuinely appreciate them for their time and commitment to ensure my academic achievement. Their advice contributed a great deal in my success. I would like to recognize Dr. Yubo Fan for his collaborative works.

I would like to acknowledge Ms. Jill Powers, Ms. Whitney Ajie, Ms. Jade Kennedy, Ms. Angie Medina and Ms. Sandy Manning for their assistance and support through all these years.

I would like to thank former group members, Dr. Amber Schaefer, Dr. Jing Liu, Dr. Andrey Malakhov, Dr. Arjun Raghuraman, Dr. Dmytro Fedoseyenko, Dr. Liangxing Wu, Dr. Cliferson Thivierge, Dr. Jiney Jose, Dr. Yuichiro Ueno, Dr. Junyan Han, Dr. Ye Zhu, Juan Rodriguez-Poirier, Orlando Flores, and especially Dr. Eunhwa Ko for their valuable friendship. Their advice and support had made all the hard work worthwhile. I also thank all current members of Burgess' group for their companionship and wish them all the best in their academic career.

In addition, I would like to pay a special thank to my family and friends both in Thailand and The United State for all the patience and support, especially Dr. Thanathorn Vajirachakorn and Dr. Panitan Kewcharoenwong.

Finally, I would like to recognize the Royal Thai Government for giving me a valuable opportunity to study in The United State and for all the support in my graduate study.

TABLE OF CONTENTS

Page

Page

LIST OF FIGURES

FIGURE Page

FIGURE Page

FIGURE Page

FIGURE Page

LIST OF TABLES

LIST OF SCHEMES

SCHEME Page

CHAPTER I
INTRODUCTION*

N-Heterocyclic carbenes and phosphines have played an important role in organic chemistry as strong binding ligands for many transition metals, especially for asymmetric catalysis.[1] Many active catalysts have been widely synthesized and studied to advantage of their unique strong σ-donors leading to advanced complexes including Grubbs olefin metathesis,[2,3] palladium C–C coupling catalysts for Suzuki–Miyaura and Heck reactions,[4] Ru-, Rh- and Ir-catalysts for asymmetric hydrogenation of alkenes.[5,6] Comparison between *N*-heterocyclic carbene and phosphine ligands have been extensively investigated to obtain comprehensive data for developing new organometallic catalysts.[7-10]

During the last decade, enantioselective hydrogenation catalysts derived from Wilkinson's $[Rh(PPh_3)_3Cl]$, Noyori's $[Ru(acetate)_2(BINAP)]$ and Crabtree's $[Ir(COD)(PCy_3)py]PF_6$ catalysts (Figure 1.1) have been synthesized to hydrogenate functionalized and unfunctionalized alkenes.[11] Research on these complexes, especially with *P*,*P*-ligands, has shown impression on stereoselective hydrogenation of tri- and tetra-substituted alkenes with coordinating functional groups (CFGs) such as amides, carboxylic acids, and alcohols.[12-15] Chiral analogs of Crabtree's catalyst, *ie N*,*P*-Ir complexes, however, have been recognized as the most useful catalyst that can use for hydrogenation of olefin without coordinating functional groups.[16-18]

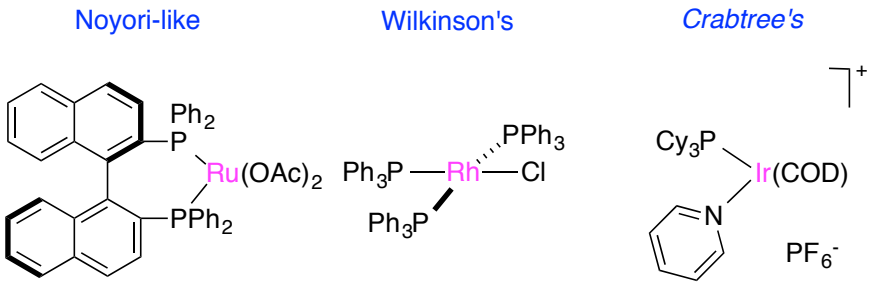


Figure 1.1. Structure of Noyori-liked, Wilkinson's and Crabtree's catalyst.

1.1 Chiral iridium catalysts for hydrogenation

Pfaltz *et al,* introduced the first chiral analogs of Crabtree's catalyst, derived from phosphines and oxazolines in 1998, that could be used for hydrogenation of various unfunctionalized olefins giving excellent enantioselectivities.[19] Moreover, this study also showed that using *tetrakis*[3,5-bis(trifluoromethyl)phenyl]borate ($BARF^-$) could improve the conversion and reduce catalyst loading as low as 0.02 mol %.[20] The study indicated that iridium complexes with this bulky and weakly coordinating anion were much less sensitive to moisture and reactions were very easy to handle without using any specially dried solvents. This study has brought major effect into a lot of research leading to new design of efficient catalysts for enantioselective hydrogenations. Figure 1.2 showed examples of chiral analogs of the Crabtree's catalyst with different *P*-ligands.[21-29]

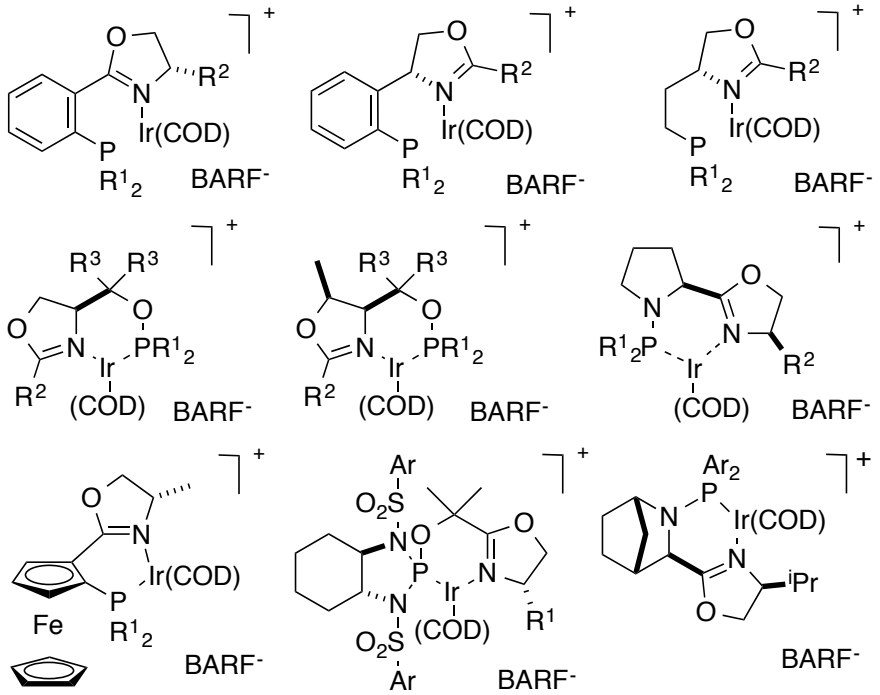
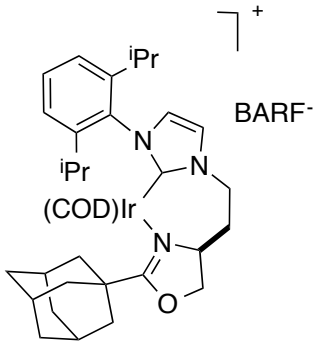


Figure 1.2. Examples of chiral analogs of the Crabtree's catalyst with different phosphine ligands.

As mentioned above, phosphine ligands have been studied in comparison with *N*-heterocyclic carbenes. The latter was considered to be "phosphine mimics" analogs. In 2001, our group reported libraries of chiral analogs of Crabtree's catalyst derived from *N*-heterocyclic carbenes and oxazolines.[30] This study introduced the first effective unfunctionalized tri-substituted alkenes hydrogenation catalyst **1** (Figure 1.3) derived from *N*-heterocyclic carbenes by substitution of phosphines with imidazolylidene.[30,31] The catalyst could hydrogenated many unfunctionalized alkenes including tri-substituted monoenes, di- and tri-substituted dienes (examples in Figure 1.4) with good conversions and excellent stereoselectivities.



(*S*)-1

Figure 1.3. Chiral analogs of the Crabtree's catalyst derived from oxazoline and *N*-heterocyclic carbenes developed by our group.

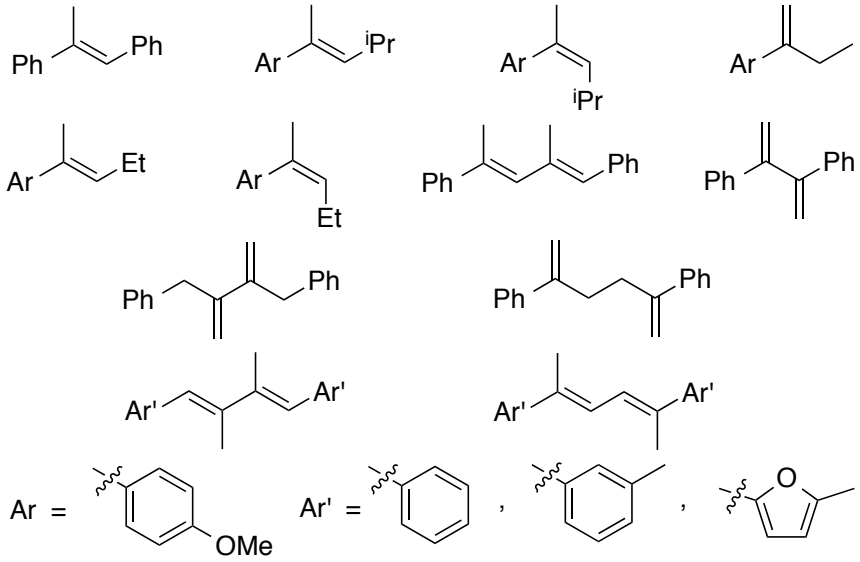


Figure 1.4. Examples of unfunctionalized alkene substrates investigated with catalyst **1**.

Mechanism of the hydrogenation reaction using chiral Crabtree's analogs was also investigated by our group[32-35] and others[36] through DFT calculations. Similar conclusions have been made that Ir(I) undergoes oxidative addition to a Ir(V) tetrahydride complex that is in a fast equilibrium with Ir(III) dihydrido-dihydrogen complex. After that, migratory insertion was occurred following by reductive elimination then repeated the catalytic cycle. (Figure 1.5)

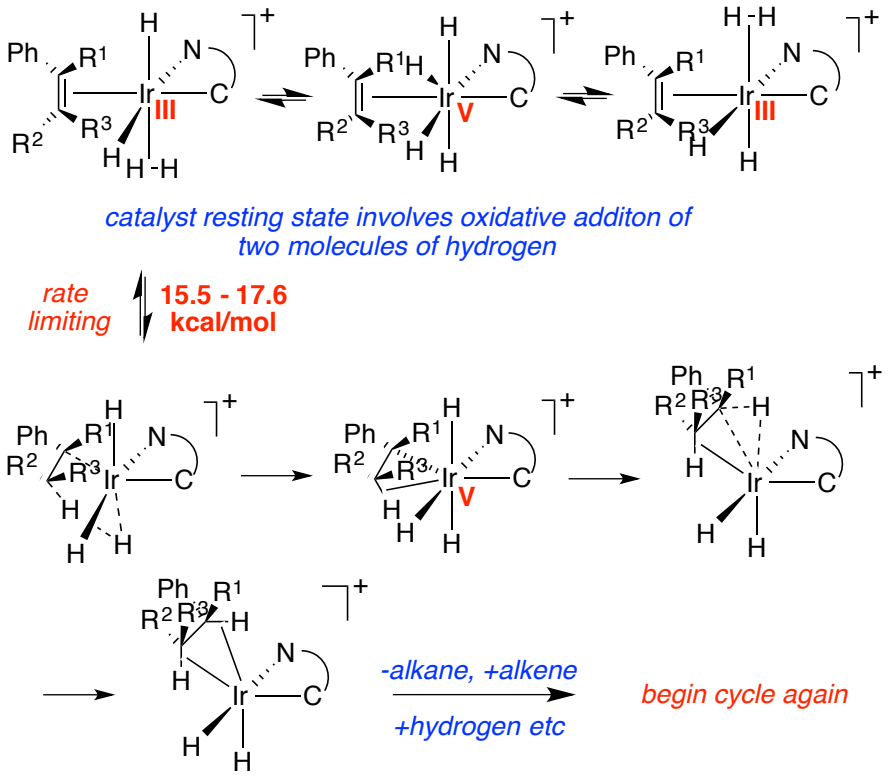


Figure 1.5. DFT calculations of iridium catalyzed hydrogenation pathways.

In addition to oxazoline-based chiral Crabtree's analogs, many hydrogenation catalysts have been synthesized using different sources of nitrogen chelating group such as pyridines, thiazoles, amides and ureas. Figure 1.6 shows examples of these catalysts. Hydrogenation of unfunctionalized alkene using these catalysts showed good conversions and enantioselectivites.[19,37-73]

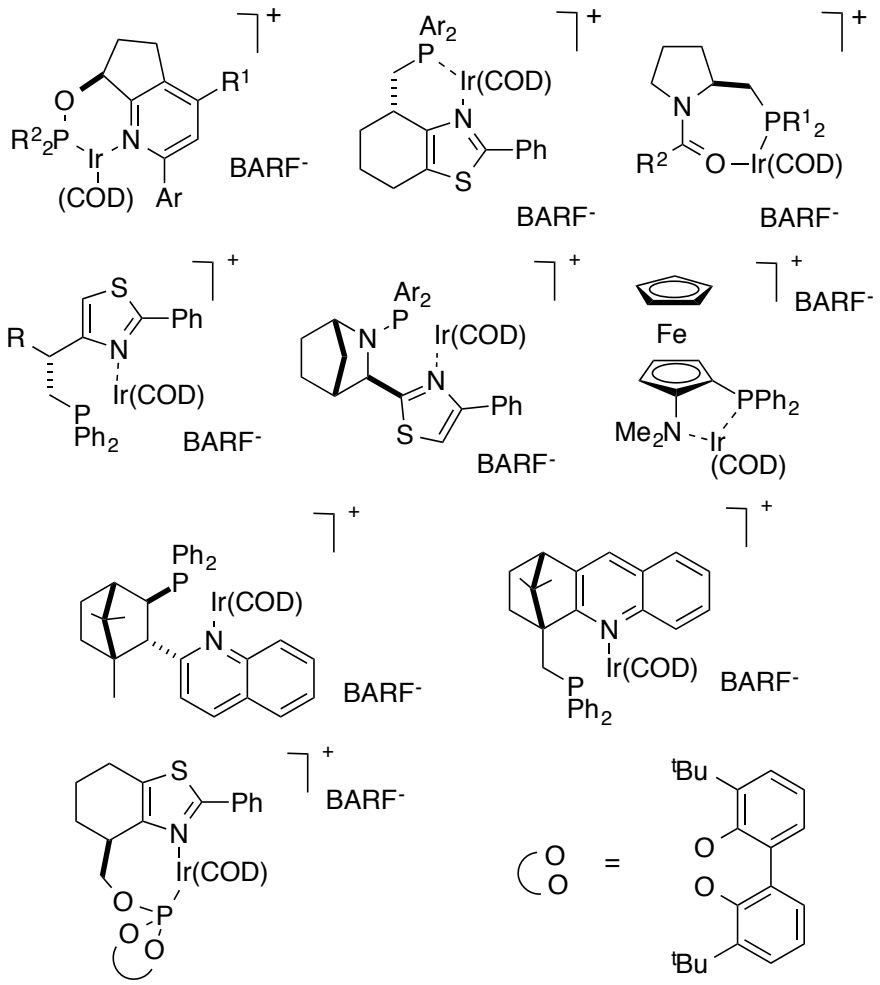


Figure 1.6. Examples of chiral analogs of Crabtree's catalyst with different sources of nitrogen chelating group other than oxazoline.

Although unfunctionalized alkenes are very unique substrates for hydrogenation using chiral analogs of Crabtree's catalyst, they have limited application because they cannot be easily modified. Therefore, research on these types of catalyst was then applied to more useful compounds that can be used as chirons or chiral building blocks. These compounds required at least one functional group (FG) that can be modified or homologated such as alcohols, acids, esters, ethers, vinyl phosphonates,[74-77] vinyl fluorides,[78,79] CF_3-substituted olefins,[80] vinyl silanes,[81] enol phosphinate esters,[82,83] enol ethers,[21,84] vinyl boronates,[85] enamines,[86-88] allyl and vinyl sulfone.[89] These chirons, except alcohols and acids, were considered to be non-coordinating functional groups, *ie*

non-CFGs, or weakly coordinating functional groups. In order to obtain more application of catalyst **1**, our group also investigated some simple alkenes other than nonfunctionalized olefins, such as tiglic alcohol and ethyl tiglate. Figure 1.7 shows examples of the simple chirons with functional group hydrogenated with chiral Crabtree's catalysts, shown in Figure 1.2, 1.3 and 1.6.

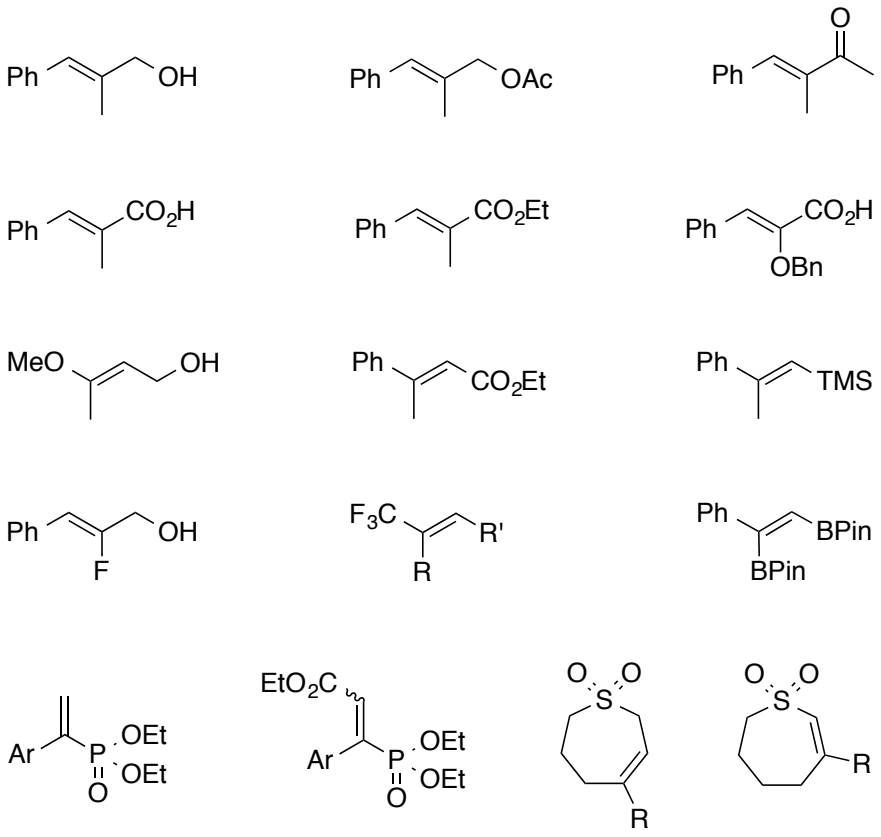


Figure 1.7. Simple hydrogenation substrates using chiral analogs of Crabtree's catalysts.

Over the last decade, our group has studied many alkene hydrogenation substrates using catalyst **1** to give useful chirons. Figure 1.8 shows the useful hydrogenation products obtained from catalyst **1**.[90]

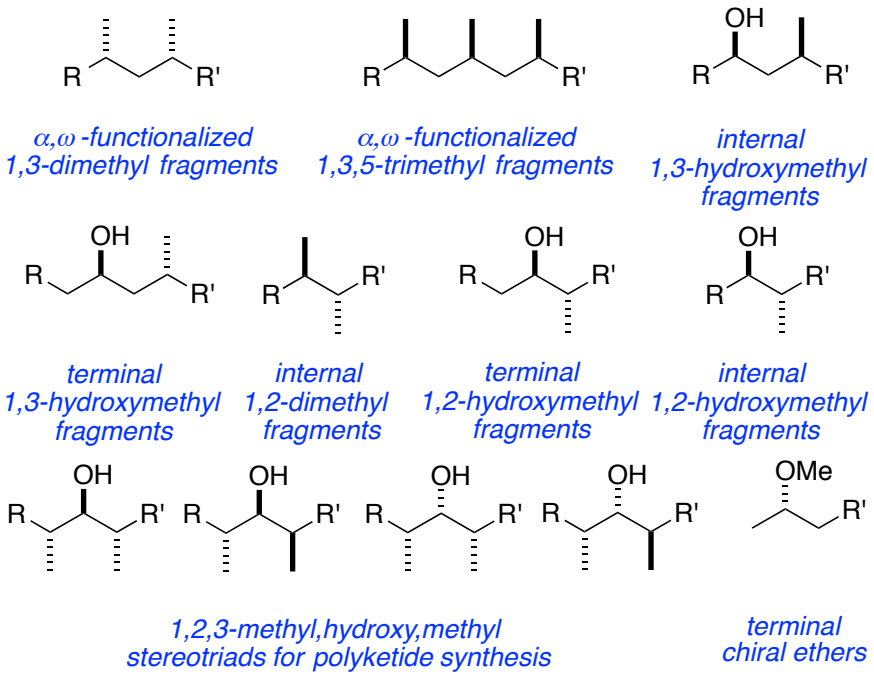


Figure 1.8. Important chirons prepared from catalyst **1**.

In addition to those shown in Figure 1.8, there are some chirons that can be used to build useful natural products that have yet to be made via alkene hydrogenations; for examples α,ω-functionalized 1,3-dihydroxy (for skipped polyols), 1,3-amino alcohols and α-methyl-γ-substituted amino acids still have not been studied especially by our catalyst **1** (Figure 1.9). Investigation of hydrogenation of alkene precursors using catalyst **1** to obtain these chirons with good stereoselectivities could complete the series and indicate more application from the chiral Crabtree's catalyst analogs. One part of my dissertation research of my Ph.D. studies is related to the application of catalyst **1** to synthesize α-methyl-γ-substituted amino acid chirons.

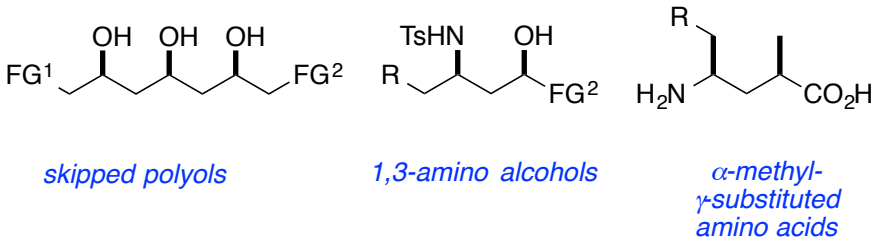


Figure 1.9. Important chirons that possible obtained from catalyst **1**.

Even though many catalysts were synthesized during the past decade, results form many studies indicated that different catalysts were suitable for different substrates; for instance, a catalyst for hydrogenation of α,β-unsaturated carboxylic ester might not be suitable for α,β-unsaturated acids and *vice versa*. Unlike other substrates, carboxylic acids were considered to be coordinated functional groups that were able to hydrogenate using Wilkinson's and Noyori's catalysts.[11] To best of our knowledge, only some chiral analogs of Crabtree's catalyst can hydrogenate these substrates with good selectivities. Figure 1.10 shows analogs of Crabtree's catalysts that can hydrogenate the carboxylic acid substrates and obtain high stereoselectivities.[55,91-95]

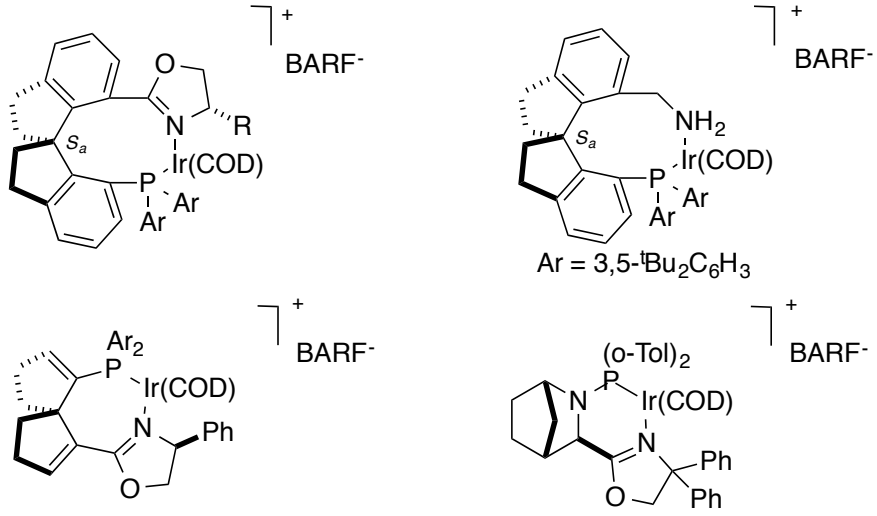


Figure 1.10. Chiral analogs of Crabtree's catalysts used to hydrogenate carboxylic acid substrates with good stereoselectivities.

In 2010, our group also used catalyst **1** to study about suitable catalyst on different substrate.[32] This study indicated that *N*,*carbene*-iridium complex, liked catalyst **1**, is less acidic than *N*,*P*-iridium complexes. Therefore, the catalyst **1** could be used to hydrogenate acid sensitive substrates, like enol ethers, without isomerization while the *N*,*P*-Iridium catalysts wasn't suitable in this case (Figure 1.11)

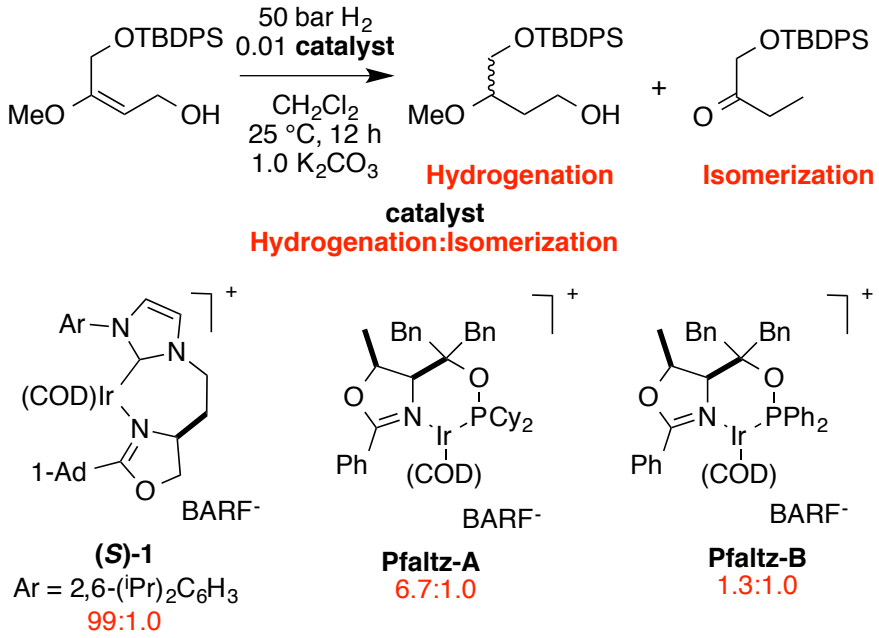


Figure 1.11. Comparison of hydrogenation of acid sensitive substrate using chiral analogs of Crabtree's catalysts **1, Pfaltz-A and -B**.

As a result from all investigation, design and synthesis of new catalysts might give opportunity to gain improvement of catalytic activity and stereoselectivity. In recent years, ligand designs based on chiral natural products have gained attention from many chemists because they are cheap and easily accessible; for instance, pyranoside phosphinite-oxazoline derivatives, synthesized from glucosamines, were introduced by Andersson' group (Figure 1.12).[56,60] The studies for hydrogenation of many di- and tri-substituted alkenes indicated that this type of complexes could be successfully applied as good hydrogenation catalysts.

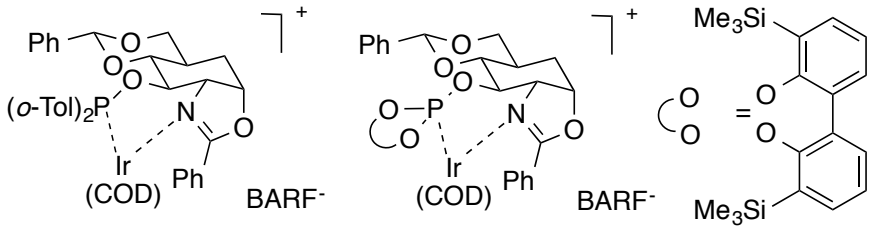


Figure 1.12. Chiral analogs of Crabtree's catalysts derived from chiral natural product, glucosamine.

According to all new ligand designs, most of my dissertation research has been related to the syntheses of new catalysts mainly for catalytic hydrogenation including the ligands derived from natural product such as cinchona alkaloids. Syntheses of new catalysts can be related to new *carbene*,*N*- and *P*,*N*-ligands as in analogs of Crabtree's catalyst, and also *P*,*P*-ligand as in analogs of Wilkinson's Catalyst.

1.2 Conclusions

Chiral analogs of Crabtree's catalyst both *carbene*,*N*- and *P*,*N*-catalysts have been introduced as a new class of asymmetric hydrogenation catalyst with excellent stereoselectivities uniquely for tri- and tetra-substituted unfunctionalized olefin. Moreover, these types of catalyst can be applied to hydrogenate mostly non-coordinating functional groups substrates including silyl ethers, enol ethers, esters, and enamines. Some of these catalysts can also be applied to substrates with coordination functional groups such as alcohols and acids. These catalysts are suitable for syntheses of many valuable chirons due to their excellent yields and stereoselectivities. Perfection of the catalysts, however, is still questionable because different catalysts are suitable to obtain excellent stereoselectivities for different substrates. Investigation of these catalysts with different chirons can increase more applications for syntheses of natural products. In addition, development of new catalysts might help improving on catalytic activities and stereoselectivities outcomes of olefin substrates. My Ph.D. research is about stereoselective hydrogenations of chiral alkenes with the *carbene,N*-Ir catalyst **1** and mainly about development of new catalysts for hydrogenations.

CHAPTER II

ASYMMETRIC HYDROGENATION APPROACHES TO γ-AMINO ACID DERIVATIVES*

2.1 Introduction

γ-Amino acids have gained attention due to their important roles in medicinal chemistry. These compounds have been explored to have biological functions, especially in nervous system. For instance, γ-aminobutyric acid (GABA) plays as the major inhibitory neurotransmitter in the central nervous system of mammals and vertebrate.[1] As shown in several studies, GABA interacts with various types of receptors including ligand-gated ion channels[96-98] and some G-coupled protein receptors.[99] GABA deficiency is associated with several psychiatric and neurological disorders, such as anxiety, depression, epilepsy and Parkinson's disease.[2] Even though GABA is the major inhibitor, it is not an efficient therapy. Low lipophilicity causes difficulty to pass through the blood brain barrier.[100,101] Consequently, lipophilic, chiral analogs of GABA have enormously investigated to provide suitable pharmaceuticals like *(R)*-baclofen,[102-104] (*S*)-pregabalin,[105-107] and (*S*)-vigabatrin.[108-110] Not only interacts with GABA receptors, some γ-amino acid derivatives, such as statine, also act as an inhibitor of aspartic acid protease which is an important part of proliferation of many diseases including AIDS (HIV protease), hypertension, malaria and Alzheimer's disease.[5]

* Reprinted in part with permission from "Asymmetric Syntheses Of α-Methyl-γ-amino Acid Derivatives", Ye Zhu, Sakunchai Khumsubdee, Amber Schaefer and Kevin Burgess, *J. Org. Chem.* **2011**, *76*, 7449-7457. Copyright 2011 American Chemical Society.

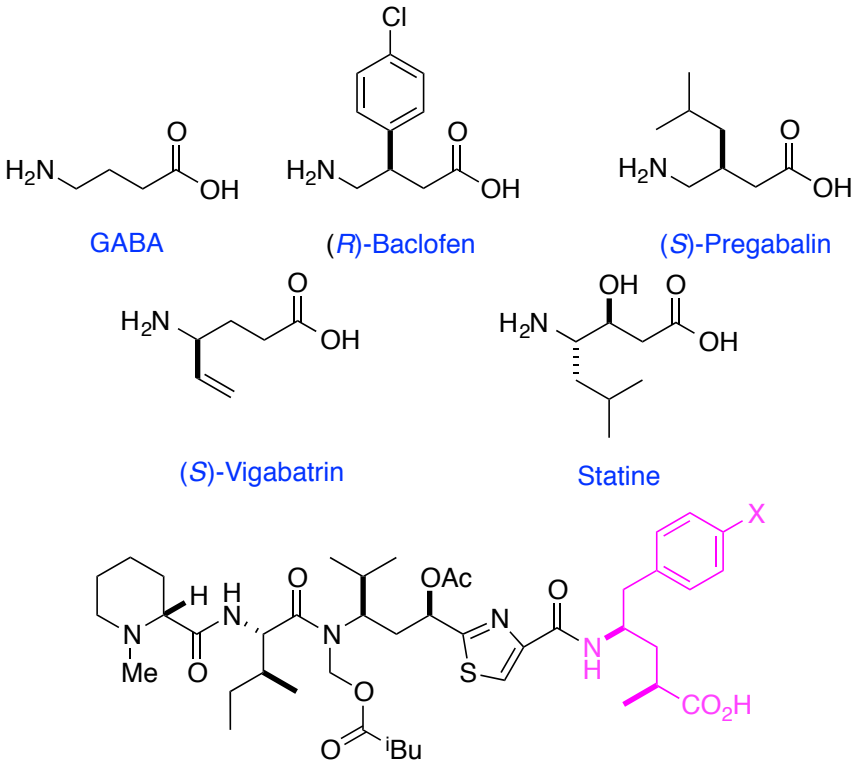
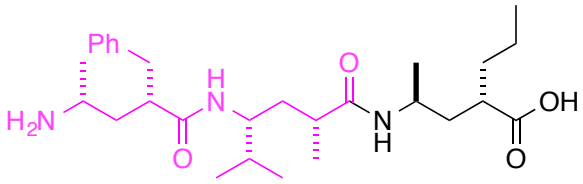
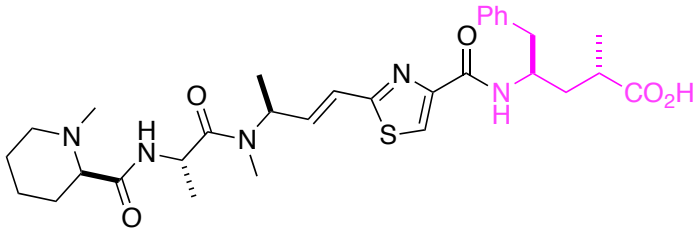


Figure 2.1. Important natural products containing optically active γ-amino acids.

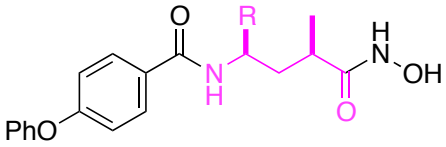
Figure 2.1 and 2.2 show examples of γ-amino acids derivatives with useful pharmacological properties.[109] Only chiral derivatives of GABA, mostly in one particular enantiomeric form, with appropriate side-chains are found in some therapeutics experiment and can selectively interact with receptors modulated by GABA, including baclofen,[111-113] pregabalin,[114] vigabatrin,[109] the experimental therapeutics in Figure 2.2, and tubulysins. Consequently, asymmetric syntheses of these fragments have been a focus of attention. Literature preparations tend to feature mostly classical methods like resolutions and diastereoselective reactions involving chiral auxiliaries.[115-117]



human peptide transporter hPepT1



antiproliferative/antitumor agent



R = CH_2OH, CH_3
matrix metalloproteinase inhibitor

Figure 2.2. Important synthetic compounds containing optically active γ-amino acids.

Moreover, many biological active compounds, as shown in Figure 2.1, contain with α-γ-disubstituted-γ-amino acids including antitumor agents and tubulysins. Figure 2.3 shows examples of syntheses the α-γ-disubstituted-γ-amino acids derivatives using chiral auxiliaries studied by Friestad's group.[116,117] Even though mechanism studies showed reactions proceeded via radical addition, the diastereoselectives were surprisingly high with up to 98:2.

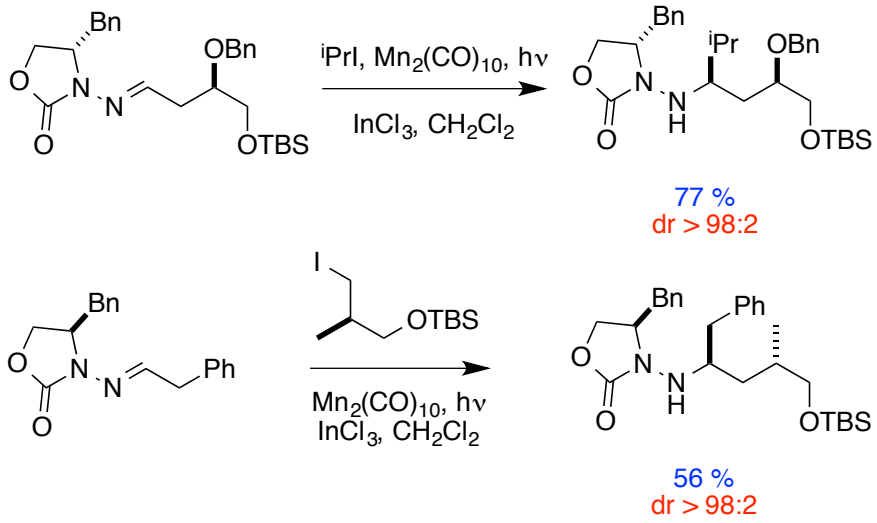


Figure 2.3. Syntheses the α-γ-disubstituted-γ-amino acids derivatives using chiral auxiliaries.

In the past decade, our group has synthesized and studied chiral analogs of Crabtree's catalyst using *carbene-oxazoline* iridium complexes. Chiral analogs of Crabtree's catalyst are special catalysts that can mediate hydrogenations of alkenes without an obvious coordinating functional group.[16,17] After many modifications of structures using different substitutents, **1** was proved to be the best catalyst for hydrogenations of many alkenes. Because catalyst development to get a new ideal ligand can be slow and unpredictable, we decided to modify the substrates (alkene geometries, protecting or functional groups) to obtain high stereoselectivities from a good catalyst. Hence, we started by modification of optically pure amino acid derivatives into appropriate alkenes (Figure 2.4). By matching the influence of our chiral catalyst **1**[30,31] with the stereochemical vectors exerted by the substrate, we hypothesized that the alkenes could be hydrogenated with high stereoselectivities.

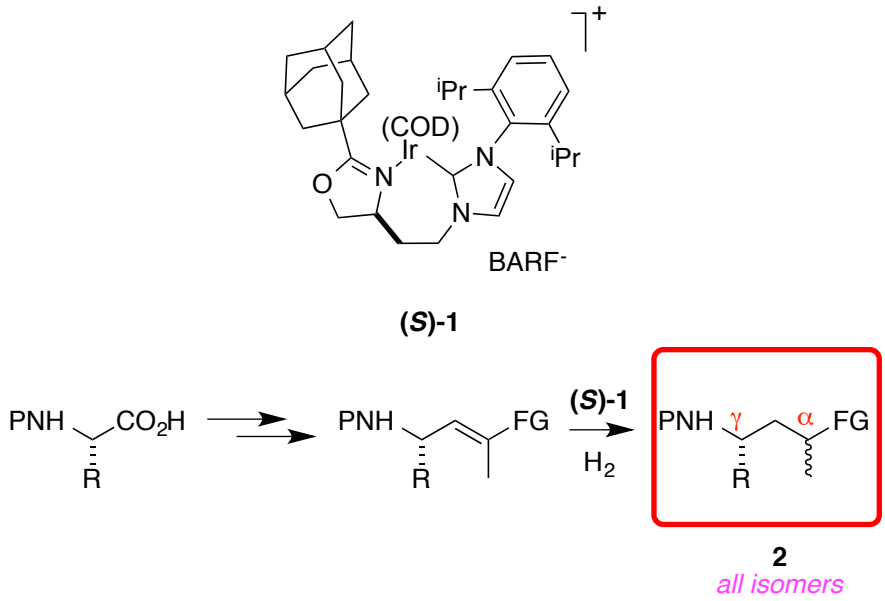
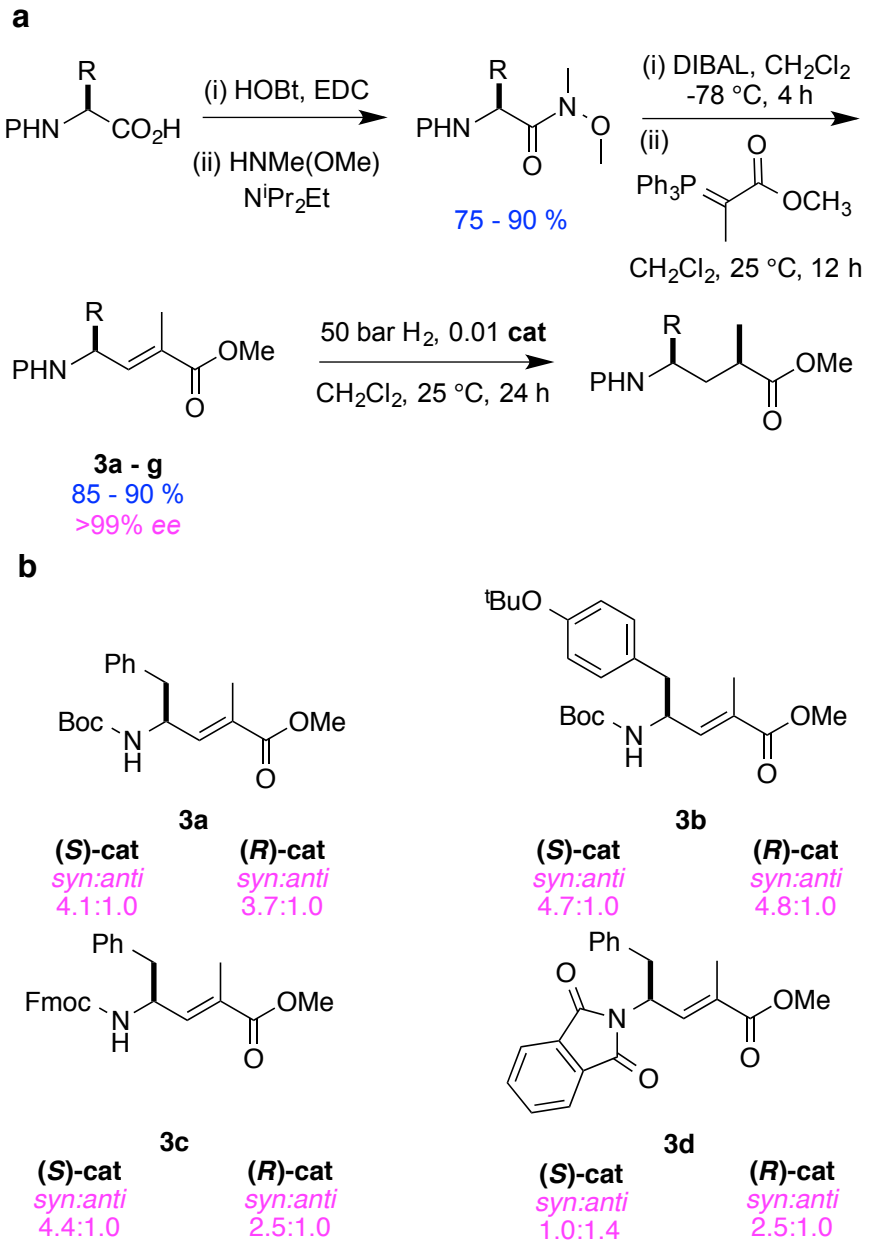


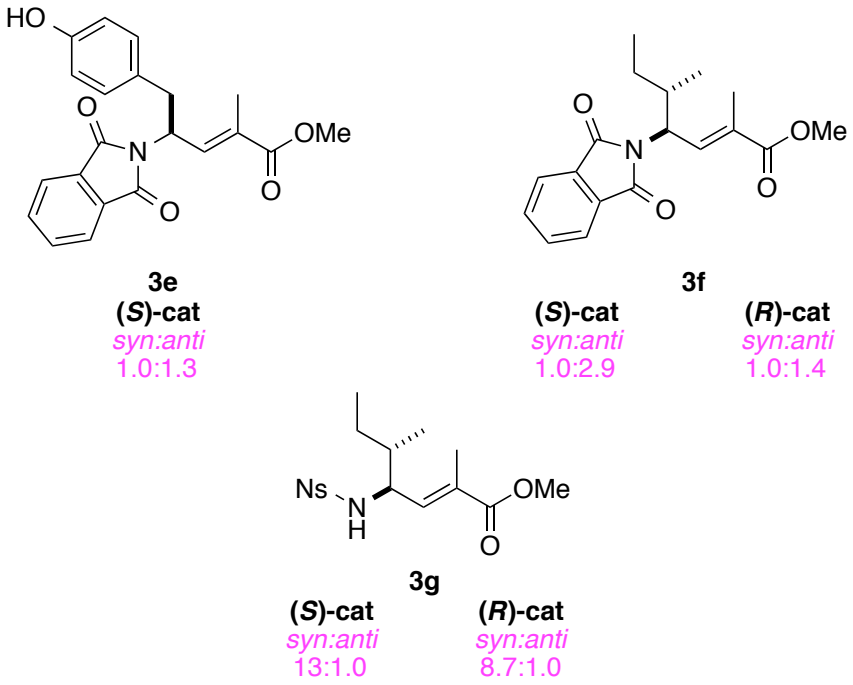
Figure 2.4. Proposed asymmetric hydrogenation of optically pure allyl amines from amino acids.

2.2 Results and discussion

Dr. Amber Schaefer, the postdoc in our research group, initiated this project by modification of *tert*-butyloxycarbonyl, fluorenylmethyloxycarbonyl, phthalyl, or nosyl (here 2-nitrophenylsulfonyl, Ns) *N*-protecting α-amino acids by converting to known[118] Weinreb amide[119] derivatives. The Weinreb amide were then reduced to aldehydes using DIBAL,[118] then immediately converted, without isolation, to allyl amines (Scheme 2.1a). These alkenes were hydrogenated using **(*S*)-1**. The best stereoselectivity of the reaction was about 13:1.0 (Scheme 2.1b). However, we hypothesized that there were possibilities to improve selectivity by modifying the substrates.



Scheme 2.1. **a** Preparation and **b** asymmetric hydrogenation of γ-aminobutenoate esters.



Scheme 2.1. Continued.

Following from those results, Dr. Ye Zhu, previous graduate student in our group who studied hydrogenation of chiral allylic alcohol derived from lactic acid,[120] compared and showed that hydrogenations of ester **A** mediated by **(*S*)-1** gave only moderate selectivity. The allylic diol substrates **B** and **C**, however, were hydrogenated with higher selectivities. As suggested from those observations, converting of γ-aminobutenoate esters **3** into similar structural substrates **D** would give better selectivity from hydrogenation (Figure 2.5).

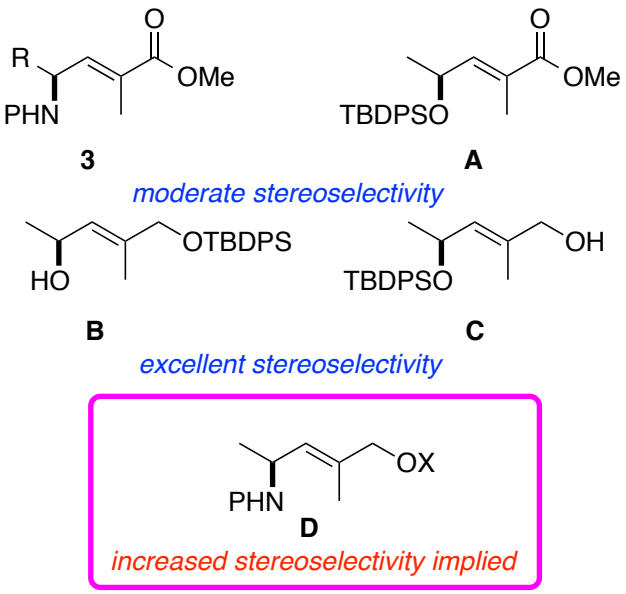
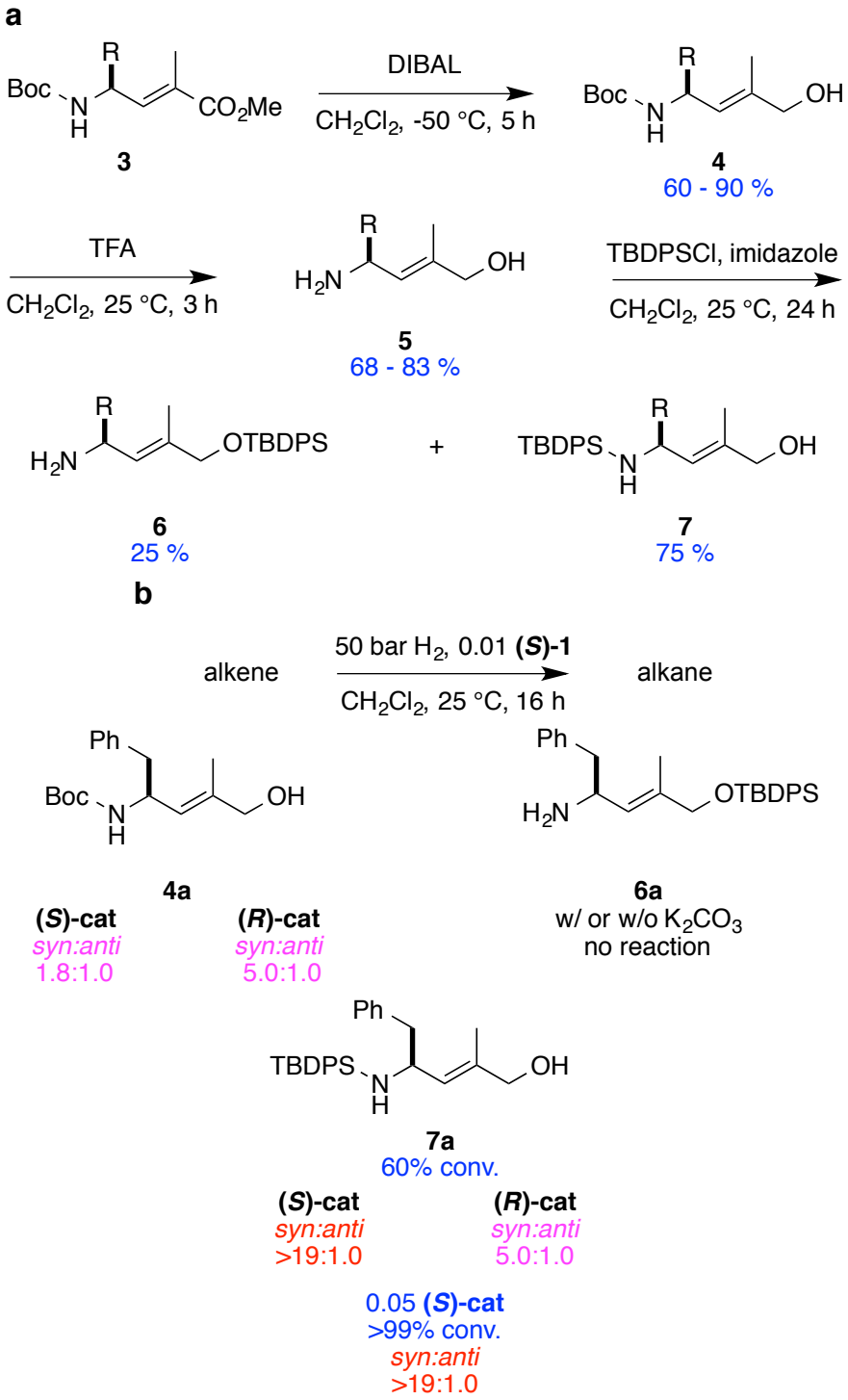


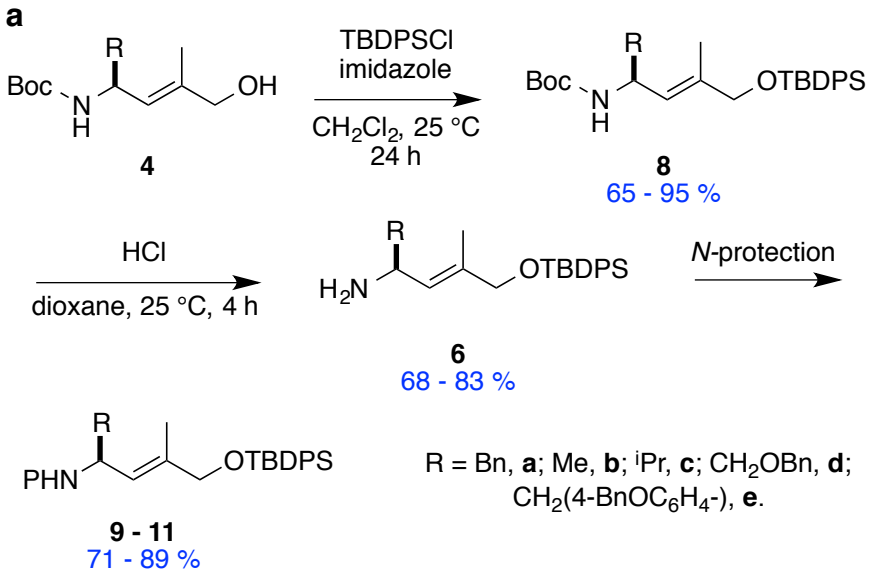
Figure 2.5. Proposed substrate modifications for enhancing the stereoselectivities in asymmetric hydrogenations.

Using phenylalanine skeleton as a based core, Dr. Ye Zhu's hypothesis was tested by reduction of ester **3a** (R = Bn) to allylic alcohol **4a**. Deprotection of *tert*-butyloxycarbonyl yielded the free amine **5a** which was converted into the bulky silyl protecting products **6a** and **7a** (Scheme 2.2a). The hydrogenation results showed moderate selectivity for **4a** but no significant conversion was obtained from free amine **6a**. Compound **7a**, however, gave an excellent selectivity by using 5 mol % of **(*S*)-1** which is little high catalyst loading in our opinion (Scheme 2.2b). Therefore, more modified substrates were synthesized to reduce the catalyst loading and to maintain the excellent selectivity.

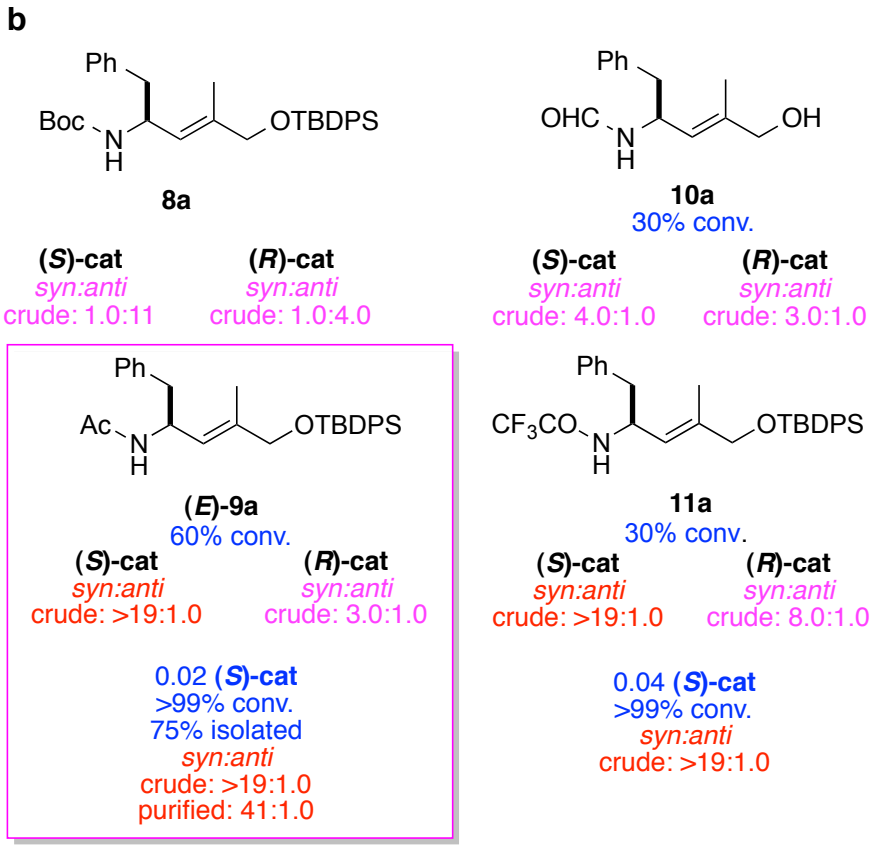


Scheme 2.2. Synthesis **a** and asymmetric hydrogenation **b** of *N*- or *O*-protected amino alcohol derivatives.

The results above indicated that protected amine can be hydrogenated with good conversions and selectivities. However, hydrogenation of formamide **10a**, which has potentially coordinating group, yielded poor conversion and selectivity. Interestingly, compound **8a** containing *N*-Boc and silyl ether gave a good selectivity in a favor of *anti* product that is opposite to other substrates discussed above. Using the results that substrates containing *N*-protected and silyl ether can be hydrogenated with good selectivities, compound **(*E*)-9a** (acetamido silyl ether) and **(*E*)-11a** (trifluroacetamido silyl ether) were synthesized and hydrogenated with excellent *syn*-selectivities. The former, however, used lower catalyst loading (2 mol %) than the latter with same selectivity. Therefore, substrate **9a** was used as core structure to provide *syn*-isomer (Scheme 2.3).



Scheme 2.3. Synthesis (**a**) *N*- or *O*-protected amino alcohol derivatives from varying α-amino acids and asymmetric hydrogenation (**b**) of *N*- or *O*-protected amino alcohol derivatives from phenylalanine.



Scheme 2.3. Continued.

To complete this series, Dr. Zhu aimed to get the *anti*-isomer. Investigation of asymmetric hydrogenation using **(*S*)-1** indicated that most reactions followed the *substrate control* that has 1,3-allylic strain effects[121] as dominant influences. Therefore, he hypothesized using *Z*-alkenes relative to their *E*-isomers should give *anti*-isomers.

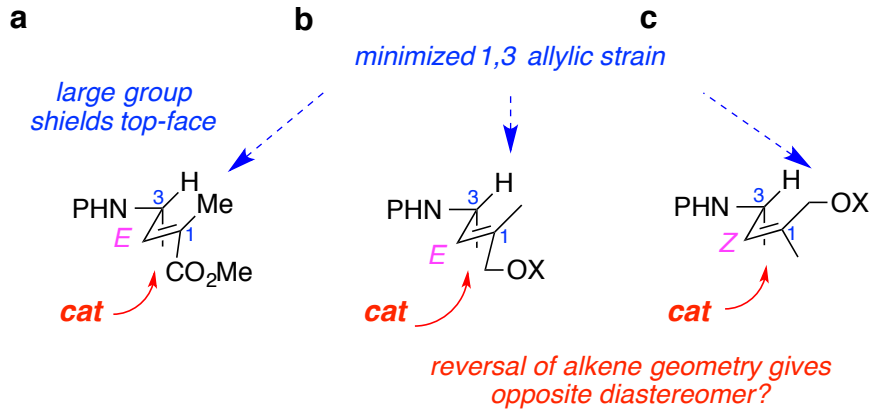
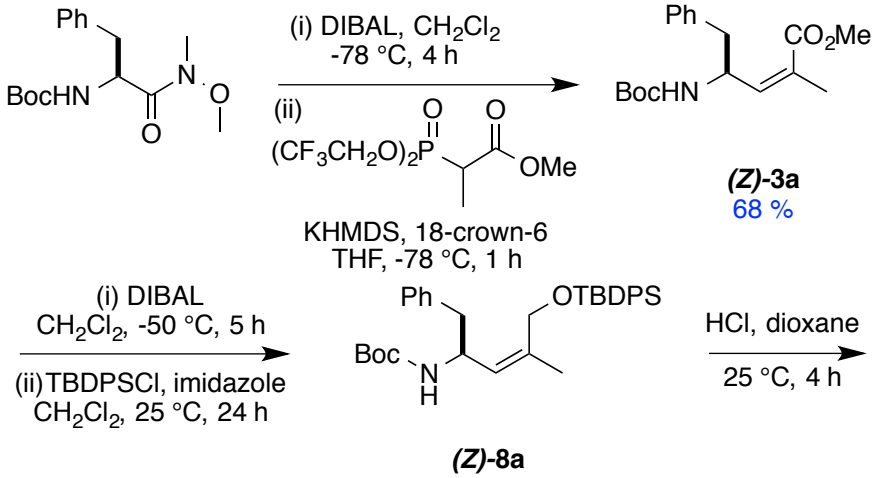
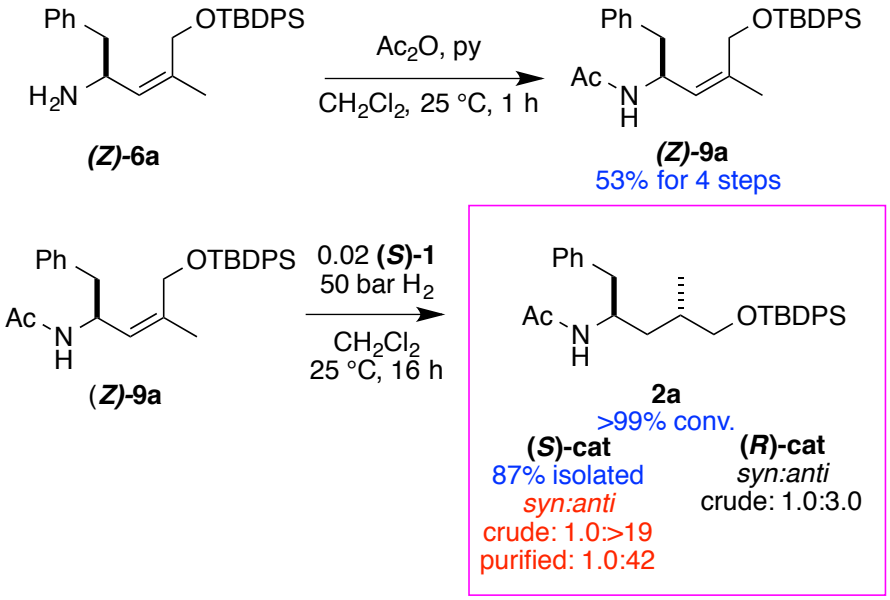


Figure 2.6. Hypothesis for obtaining the *anti*-skeletons of α-methyl-γ-amino acid derivatives.

Z-Allylic alcohol was synthesized starting from reduction of the same Weinreb amide following by the Still-Gennari reaction to give **(*Z*)-3a**.[122] Reduction and *N, O*-protections give **(*Z*)-9a** overall about 53 %. Without further modification, the results indicated that using 2 mol % of **(*S*)-1** gave *anti*-isomer with very good diastereoselectivity.



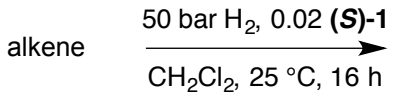
Scheme 2.4. Synthesis and hydrogenation of (***Z***)-**9a**.

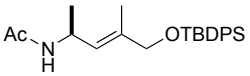
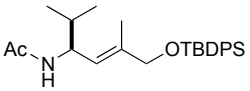
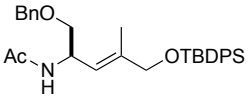
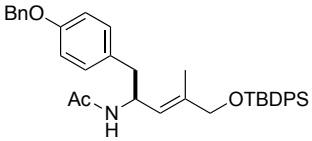
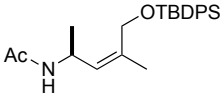
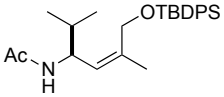
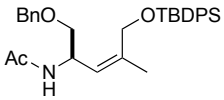
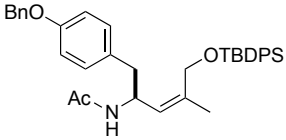


Scheme 2.4. Continued.

As the *syn*- and *anti*-isomers were completed, my part in this project was to prove that this method could be expanded to other allylic amines based on the different amino acid starting materials with the correct stereochemistry of the final products. The amino acid side-chains (alanine, serine, tyrosine and valine) were chosen from the useful biological active compounds as shown in Figure 2.1 and 2.2. As a result, (*E*)- and (*Z*)-forms of **9b – e** were prepared by following the sequences used for (*E*)- and (*Z*)-forms of **9a**. Table 2.1 shows the results obtained from hydrogenations gave excellent conversions and diastereoselectivities.

Table 2.1. Hydrogenation of various α-substituted alkene substrates using **(*S*)-1**



9	R	*syn:anti*[a,b] crude	*syn:anti*[a,b] purified	isolated yield (%)
(*E*)-b		19:1.0	39:1.0	90
(*E*)-c		49:1.0	49:1.0	91
(*E*)-d		12:1.0	40:1.0	75
(*E*)-e		24:1.0	43:1.0	89
(*Z*)-b		1.0:9.0	1.0:40	72
(*Z*)-c		1.0:19	1.0:43	83
(*Z*)-d		1.0:11	1.0:38	73
(*Z*)-e		1.0:18	1.0:49	83

[a] Determined via HPLC on an unbonded silica 300 Å. [b] Stereochemistry was determined by comparison with known compound.

In order to confirm the stereoselectivity, alcohols **12a** and **13a** are known compounds.[117,123] The stereochemistry of samples obtained from phenylalanine was determined by comparing ^{1}H NMR spectra of these two materials.

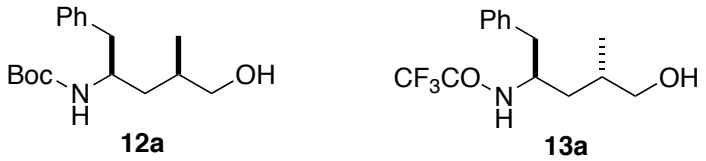
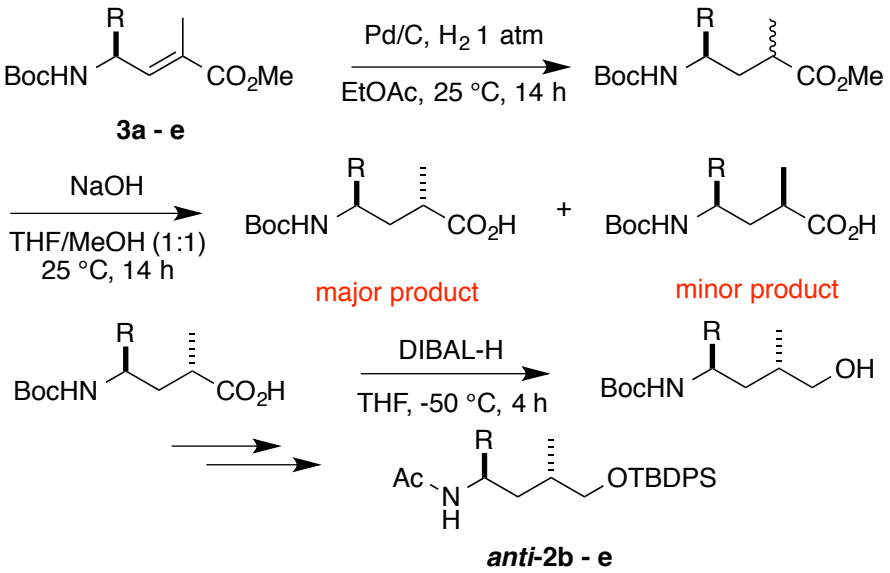


Figure 2.7. Hypothesis for obtaining the *anti*-skeletons of α-methyl-γ-amino acid derivatives from phenylalanine.

To confirm the selectivity of other α-methyl-γ-amino acid derivatives, alkenes **3b – e** were hydrogenated using Pd/C and H_2 under atmospheric pressure to give mixtures of *syn* and *anti*-esters. This mixture of esters was hydrolyzed and recrystallized to yield the pure *anti*-diastereomer as confirmed by comparing spectral data with them in the literatures.[124-127] The pure *anti*-diastereomer was reduced to corresponding alcohols, *O*-TBDPS protected and the *N*-Boc group was removed (as shown in Scheme 2.2 and 2.3). Finally, *N*-acylation gave the pure *anti*-amino alcohol derivatives **2b - e**. These compounds were then used as standards to compare (typically by HPLC) with the hydrogenation products formed using **(*S*)-1**.



Scheme 2.5. Syntheses of standard for pure *anti*-isomers.

2.3 Conclusions

In summary, we introduced the new method to synthesize α-methyl-γ-amino acid derivatives from catalytic hydrogenation reactions of allylic amines using *N,carbene* iridium catalyst. The results indicated that hydrogenation of this chiron using **(*S*)-1** gave excellent conversions and diastereoselectivities for both *syn*- and *anti*-isomers. Moreover, the method can be applied to different amino acid side-chains that have the same chiron which gave another alternative way to synthesize pure chiral compounds. The alkane products can be further applied in the part of biological active compounds in a few steps.

Moreover, we found that modicafication of substrates by playing with substrate geometries, functional groups and protecting groups are easier way to obtain stereoselective compounds than one to modify the catalyst which sometimes cannot be predictable outcomes.

CHAPTER III
HOMO-ROCHE ESTER DERIVATIVES BY ASYMMETRIC HYDROGENATION AND ORGANOCATALYSIS

3.1 Introduction

Roche ester derivatives **E** are some of the most widely appreciated chirons in organic syntheses[128-131] because such compounds have both terminal functional groups that allow modification and homologation in bidirections, especially for incorporating methyl-substituted chiral centers. It seems logical that the homologous chirons **F** would be similarly useful as chirons **E** if they were more readily available. For the purposes of this study we refer to the generic class of fragments **F** as *homo-Roche ester* derivatives.

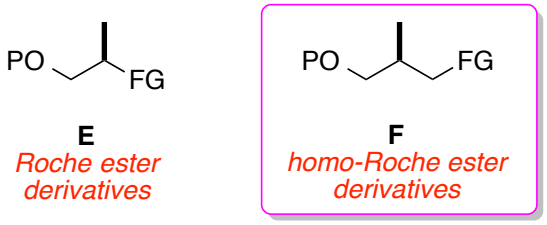


Figure 3.1. Structure of Roche ester and *homo*-Roche ester derivatives.

Scalable syntheses of chirons **F** have not gained much attention in the literature. The most directing route should be a homologation of the parent chirons **E**[132] which is probably *not* the best option to obtain chirons **F**, even though they only contain one more skeletal carbon than **E** because the Roche ester is not a cheap starting material; small quantities tend to cost more than $1 per gram. Another approach is via asymmetric hydrogenations of itaconic acid or the corresponding diesters to give the C_5-building blocks **G**.[133,134] Bidirectional homologation of chirons **G** requires efficient chemoselective modification of one of the two esters; we are aware of only one method for doing this, and it features a relatively expensive lipase in a chemoenzymatic hydrolysis to achieve a pure single monoester.[133] It is possible to instead begin with a *mono*ester of itaconic acid and hydrogenate that, but in fact the enantioselectivities for

this process tend to be less than the diacid or the diester.[133,135] Alternatively it is possible to begin the syntheses with monoesters of itaconic acid, and indeed some of these are commercially available. However, these starting materials are expensive so, overall, it is better to avoid this strategy. Any strategy that uses hydrogenation of itaconic acid, in fact, is vulnerable to the types of deactivation pathways that have been documented previously.[136,137] Another route to chirons **I** is via asymmetric additions of cuprates to α,β-unsaturated thioesters.[138]

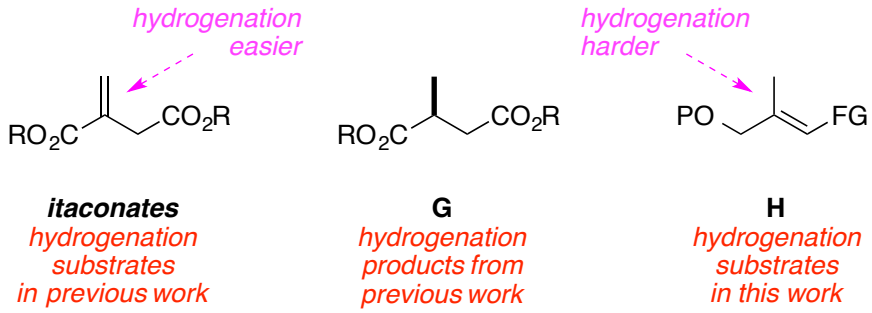


Figure 3.2. Hydrogenation substrates to obtain compound **G**.

Both the hydrogenation syntheses of chirons **F** described above feature bisphosphite complexes formed from $Rh(COD)_2^+$ *in situ.* Hydrogenation of type **H** trisubstituted alkenes would give products that are chemically related to **G**, but these types of transformations tend to be difficult to achieve using RhP_2 complexes because the double bonds are hindered.[11] In fact, the preferred catalysts for the trisubstituted alkenes **H** tend to be *N,P*-Ir complexes, *ie* chiral analogs of Crabtree's catalyst.[11] Consequently, my work in this project was to use our particular chiral analog of Crabtree's catalyst, **(*S*)-1**,[30,31] to reduce **H** -type substrates via scalable transformations to obtain single enantiomer of chirons **H**. The hydrogenated product was then further applied to obtain all stereoisomeric forms of the 2-substituted chirons **I** via organocatalytic modifications of the *homo-Roche* ester derivatives **F** which was done by Hua Zhou, another graduate student in our group. Similar reactions of achiral substrates

via organocatalytic are well known, but finding appropriate organocatalysts to overcome the stereochemical bias exerted by the C^3 chiral center was an open issue.

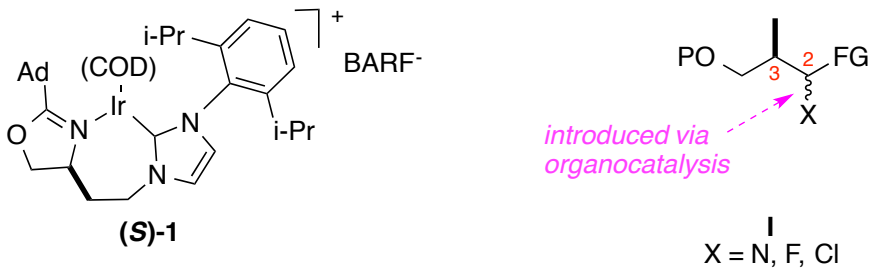
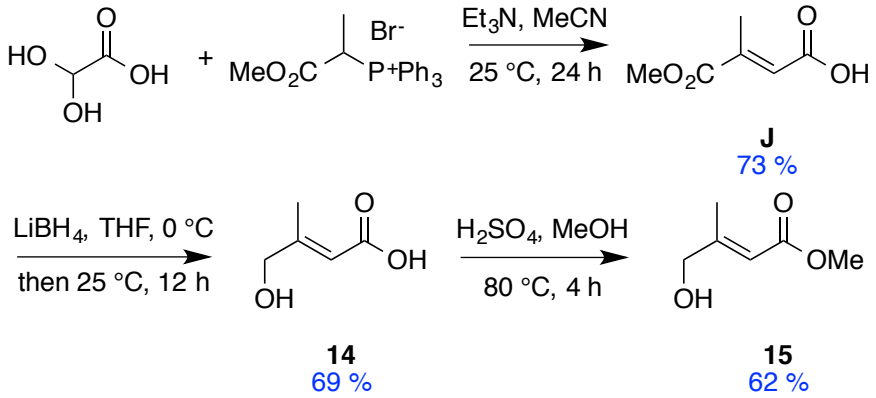


Figure 3.3. Structure of catalyst **(S)-1** used for hydrogenation and general structure of organocatalysis product **I**.

3.2 Results and discussion

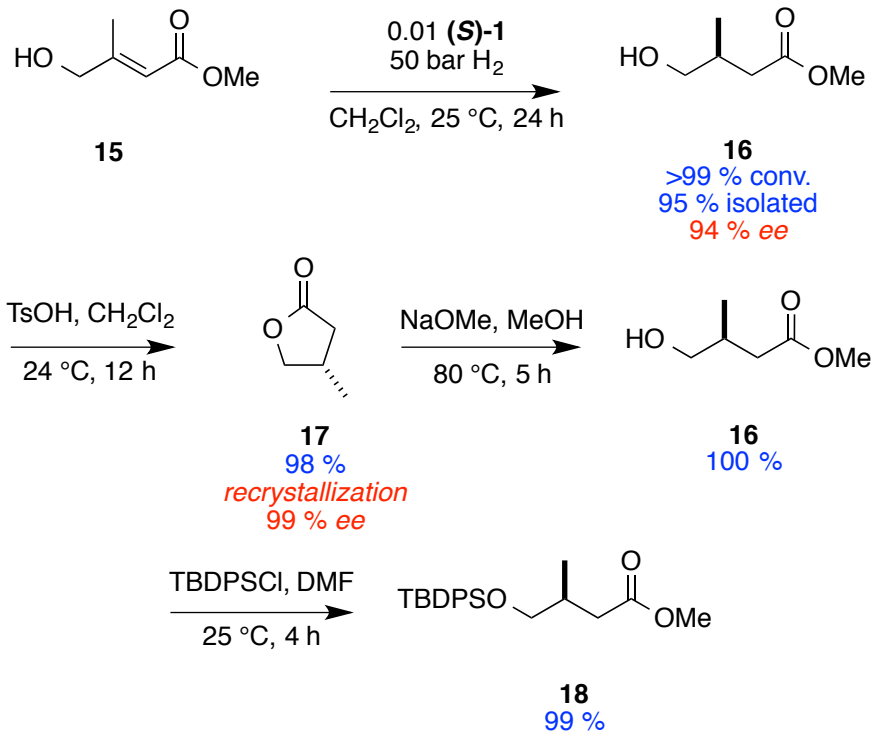
3.2.1 Synthesis of hydrogenation substrate

Following a literature procedure, glyoxylic acid monohydrate was converted to the α,β-unsaturated ester **J**.[139] The first new step in this work was to chemoselectively reduce the ester group of **J** in the presence of its carboxylic acid functionality[140] to give the hydroxyacid **14**[141,142] which was isolated via acid-base extraction.[141,142] Subsequently, the hydroxyacid **14** was esterified to give the known[143] hydroxyester **15**. None of the steps described in Scheme 3.1 involve column chromatography, and the synthesis can give tens of grams of the product **15**.



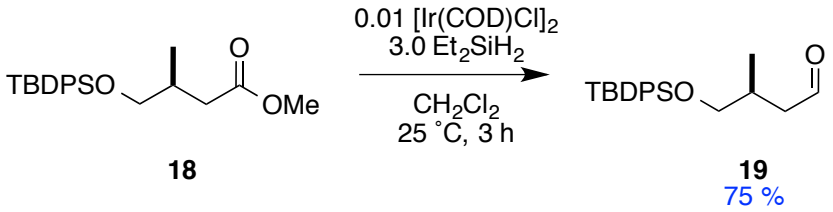
Scheme 3.1. Scalable Synthesis of the hydrogenation substrate **15**.

Hydrogenation of alkene **15** is the key transformation in this project (Scheme 3.2). Under the conditions shown in Scheme 3.2, approximately 15 g of the hydroxyester **15** can be hydrogenated with complete conversion to give **16** (a type **F** chiron), and the catalysts are still active at the end of this transformation. Even though the hydrogenation worked perfectly, only high, but not perfect, enantioselectivities were obtained. The acyclic product **16** was then lactonized to **17** then efficiently recrystallized under cold conditions to give optically pure material. For subsequent applications of these products (here and perhaps elsewhere), the lactone **17** was converted to two other potentially useful acyclic chirons, the alcohol **16** (now as one enantiomer) and the silyl ether **18**.



Scheme 3.2. Asymmetric hydrogenation of alkene **15**, then recrystallization and TBDPS-protection to obtain ester **18**.

The ester **18** was given to Hua Zhou, another graduate student in our group, to perform the application via organocatalysis as described below in this chapter. To obtain an aldehyde **19**, the ester **18** was reduced using Brookhart's catalytic silylation/hydrolysis procedure[144] (reaction 3.1). This reduction afforded the aldehyde **19** in good yield for elaboration via organocatalytic processes involving iminium and enamine intermediates.



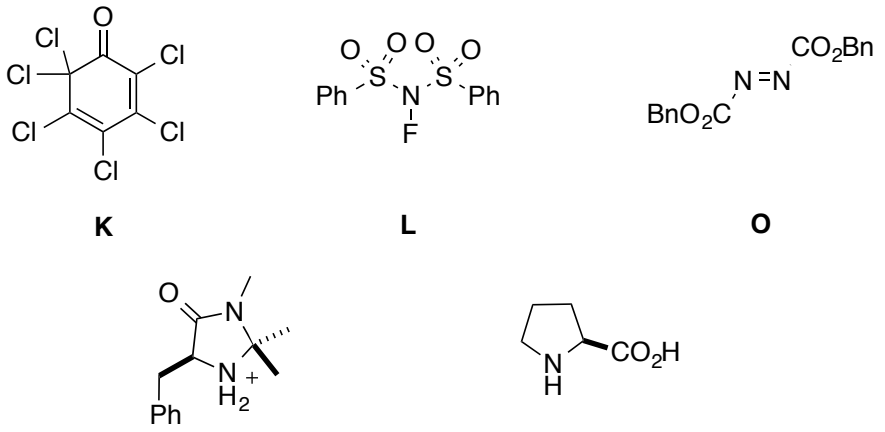
18 **19**
75 %

reaction 3.1

3.2.2 Application with organocatalysis

To the best of our knowledge, organocatalytic transformations of the *homo-Roche* aldehydes **19** have not been reported before. However, there is precedent for electrophilic α-substitutions of β-chiral aldehydes,[145] and, of course, a great deal of literature for the parent reactions of acyclic non-chiral aldehydes.[146] Catalysts and reagents for the organocatalytic transformation were chosen from a known literature[147-149] for each particular electrophiles then applied them to *homo-Roche* ester **19**.

catalysts and reagents

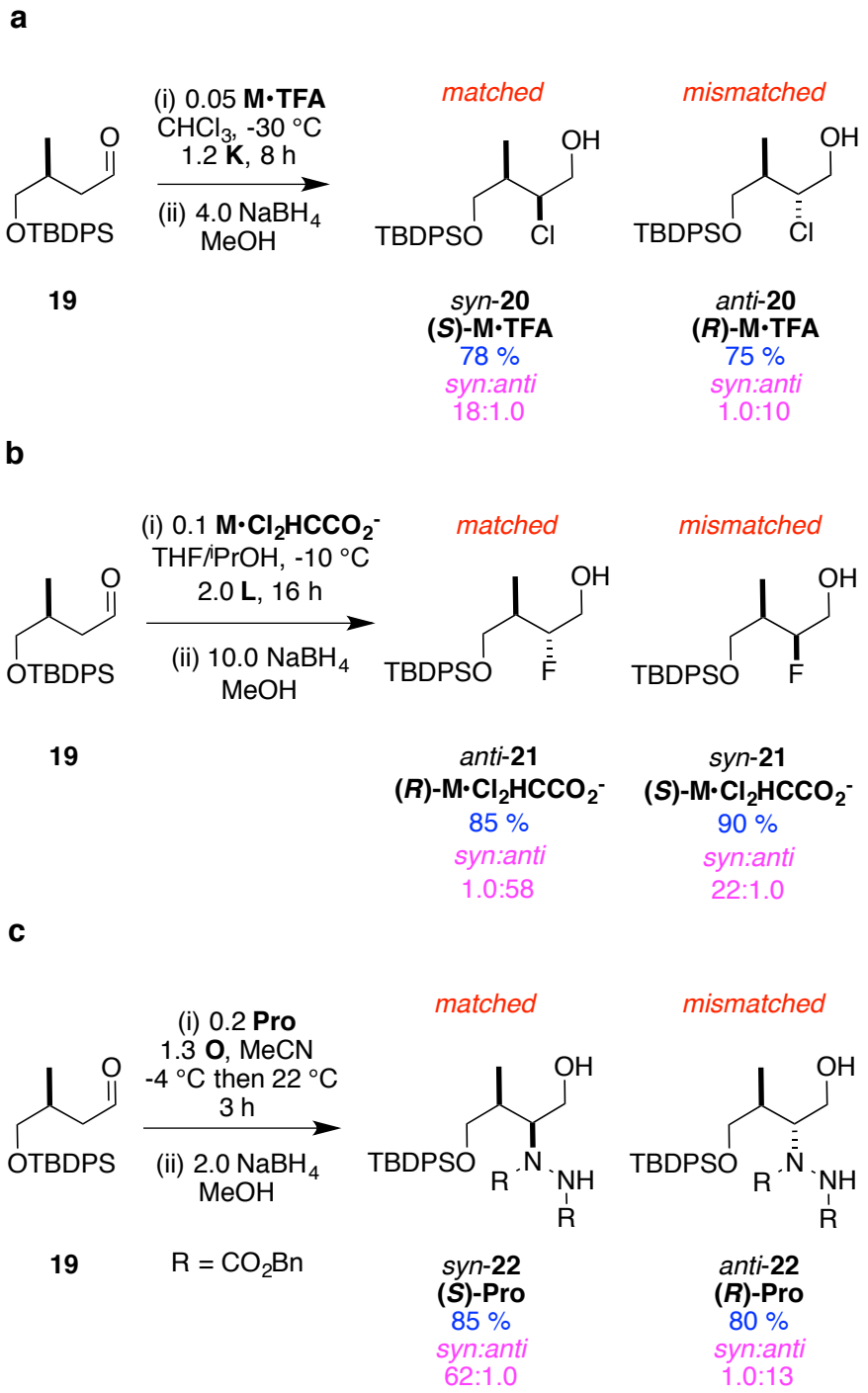


K **L** **O**

(*S*)-M **(*S*)-Pro**

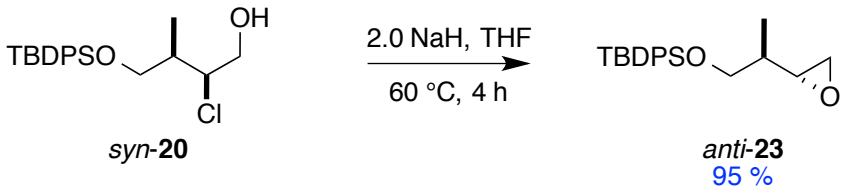
Figure 3.4. Catalysts and reagents used in organocatalysis.

Scheme 3.3 shows the data accumulated for the organocatalytic transformations of aldehyde **19**. Part **a** refers to chlorinations performed using MacMillan's catalyst **M•TFA**[150] (a commercial sample of the hydrochloride catalyst did not work in this reaction, so it was converted to the trifluoroacetate, *ie* the salt used by MacMillan's group). It emerged that the (*S*)-enantiomer of the catalyst matched[147] the substrate bias and gave an excellent stereoselectivity for the *syn*-isomer of **20** after borohydride reduction. However, in the mismatched case **(*R*)-M•TFA** overwhelmed the substrate bias hence a 10:1.0 ratio in favor of *anti*-**7** was observed. Similarly, MacMillan's fluorination procedure[148] using **(*R*)-M•$Cl_2HCCO_2^-$** gave even better matched and mismatched selectivities in catalyst-controlled reactions to give the 2-fluoroalcohols **21** after reduction. For amination reactions it was desirable to use d*ibenzyl* azocarboxylate rather than other alkyl derivatives for the reasons indicated below (Scheme 3.4), so we used List's procedure that described application of exactly that electrophile.[149] Just as in the chlorination and fluorination reactions, the aminations were catalyst-controlled. These transformations gave superb selectivity in the matched case for *syn*-**22**, and a 13:1.0 ratio for the *anti*-isomer via the mismatched process.



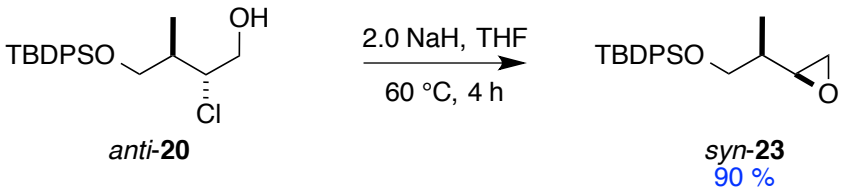
Scheme 3.3. Asymmetric transformations of substrates **19**: **a** chlorination; **b** fluorination; and, **c** amination. Throughout, selectivities were determined via analytical HPLC on a Chiralcel-OD column.

Reactions 3.2 and 3.3 showed how the isomeric 2-chloroalcohols **20** were efficiently ring closed to the corresponding epoxides **23**. These reactions were performed because the epoxides **23** are valuable chirons, but their use has been limited by the fact that syntheses of these materials require multiple steps and some routes are only practical for one or two of the four possible stereoisomers.[151-153]



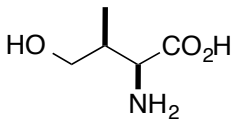
syn-**20** *anti*-**23**
95 %

reaction 3.2



anti-**20** *syn*-**23**
90 %

reaction 3.3

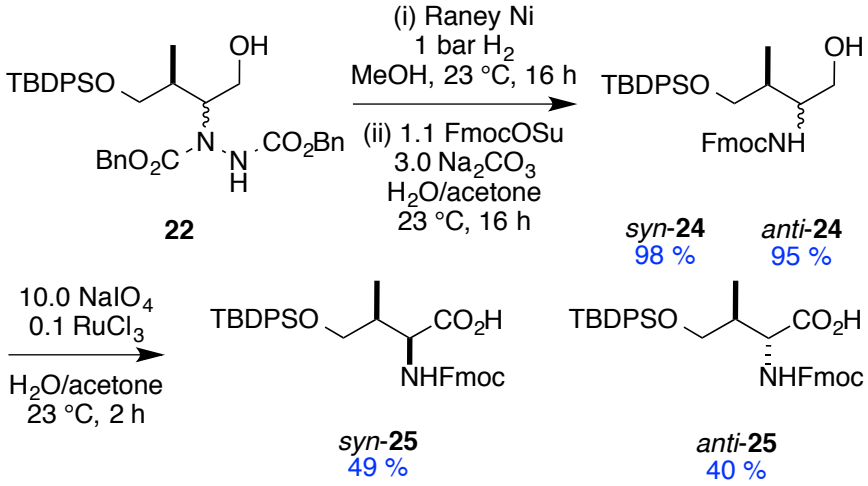


P

Figure 3.5. Structure of derivatives of γ-hydroxyvaline **P**.

Finally, derivatives of γ-hydroxyvaline **P** (Figure 3.5) were prepared to illustrate how the amination products **22** could be used in a novel short synthesis. γ-Hydroxyvalines are naturally occurring amino acids that have been associated with stimulation of insulin secretion.[154] Hydrogenolysis of the benzyl protecting groups of **22** and simultaneous homolysis of the *N*-*N* bond gave the *N*-protected amino alcohols **24** after addition of Fmoc (Scheme 3.4). Catalytic oxidation of those alcohols gave the *N*-Fmoc-γ-silyl protected amino acid **25**. All four stereoisomers of **25** could be obtained

using this route, and one enantiomer of each of the *syn*- and *anti*-forms was made to prove this. The final products **25** are suitably protected for many peptide synthesis strategies, so no attempt was made to obtain the corresponding γ-hydroxyvalines since we have no immediate application for these. The synthesis of the 2*S*,3*S*-*syn*-isomer was performed on a large enough scale to obtain 0.42 g of product. Previous syntheses of γ-hydroxyvaline derivatives required either 12 steps to obtain an enantiomer of the *N*-BOC-*O*-PMB-protected form of the reduced product (*ie* alcohol not carboxylic acid),[155] or via multistep routes to *syn*,*anti*-mixtures of various protected derivatives that were then separated (via crystallization of diastereomeric copper complexes,[156] or via column chromatography[157]).



Scheme 3.4. Syntheses of α-*N*-γ-*O*-protected forms of γ-hydroxyvaline

3.3 Conclusions

The pivotal observation in this paper is that we may use type-**H** trisubstituted alkenes, specifically **15**, to give the same product that would be formed from hydrogenation of itaconic acid (or the diester) *and* differentiation of the two carboxylate groups (then reduction). Key to this study is the fact that chiral Crabtree's analogs like **(S)-1** can mediate hydrogenations of trisubstituted alkenes without suitable coordinating

functional groups (CFGs) for binding Rh-centers. Fortunately, the starting material **18** is also easy to make and this facilitates the whole process.

Prior to our studies, Alexakis and Mazet elegantly combined enantioselective iridium-mediated isomerization reactions[158-161] with organocatalytic functionalization of aldehydes to form two chiral centers.[145] The work we have performed here is conceptually similar except that it is based on production of a particularly high-value chiron, the *homo-Roche* ester, and elaboration of that in distinct steps. Moreover, the initial chiral center is established here via hydrogenation rather than isomerization reactions.

CHAPTER IV
A COMPARISON BETWEEN OXAZOLINE-IMIDAZOLINYLIDENE, -IMIDAZOLYLIDINE AND -BENZIMIDAZOLYLIDENE HYDROGENATION CATALYSTS*

4.1 Introduction

Since *N*-heterocyclic carbenes were introduced, they have been used extensively, especially in catalytic reactions. Different types of *N*-heteroocyclic carbenes have been synthesized and compared in both steric and electronic effects. Steric effect of *N*-heterocyclic carbenes have been usually compared by varied *N*-substituents substrates with different alkyl or aryl groups. Comparison of their electronic effect can use the same method or it can be compared by changed core structure of *N*-heterocyclic carbene such as ligand **a** – **c** (Figure 4.1).

Stereoelectronic variation is to be expected within the series of *N*-heterocyclic carbene ligands **a** – **c**.[162,163] With respect to size, even members of this series with the same *N*-aryl substituents may have various steric influences because they have different flexibilities; for instance, the planar systems **b** and **c** are less flexible than the saturated one **a**.[162] Flexibility in the ligands can also indirectly affect their electron donating properties. Direct donation of π-electrons from the *N*-aryl substituents to the metal in these systems is significant,[9,164] and it is bound to be orientation dependent. Consequently, differences in the carbene core that perturbs the preferred orientations of the aryl groups also modulate the electron densities they donate to the metal.[165] Moreover, the saturated imidazolinylidene **a** is the only member of this series that is not aromatic and this has ill-defined impacts on its electron donating properties relative to the other two.[1]

---

* Reprinted in whole with permission from "A Comparison between Oxazoline-imidazolinylidene, -imidazolylidine, -benzimidazolylidene Hydrogenation Catalysts", Sakunchai Khumsubdee, Yubo Fan and Kevin Burgess, *J. Org. Chem.* **2013**, *78*, 9969-9974.

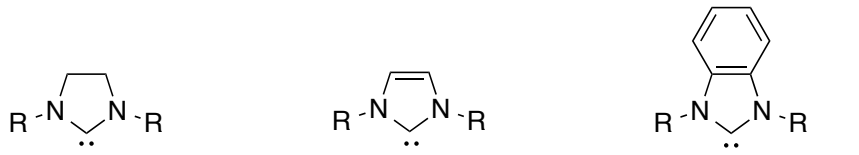


Figure 4.1. Core structure of *N*-heterocyclic carbenes, imidazoline, **a**; imidazole, **b** and benzimidazole, **c**.

Several strategies have been devised to gauge stereoelectronic differences in the series of ligands **a** – **c**. These approaches consider dimerization of the parent carbene,[166] IR and Raman spectra[7] of CO ligands in the same complex (sometimes interpreted in terms of the Tolman electronic parameter),[8] electrochemical studies,[9] and theoretical approaches.[10] Overall, the most general conclusions from these studies are that all three ligands are stronger σ-donors than any phosphine, but electronic effects within the series tend to be small.[10,162] For instance, carbonyl complexes containing ligands **a** - **c** may have IR absorbance within 3 cm^{-1} of each other, while others have almost identical REDOX potentials.[9]

Even if electronic variability in the series **a** – **c** is small, and the *N*-aryl groups are identical, substitution of one of these ligands for another one can have significant effects on *catalytic* performance. Evidence for this assertion comes from the Grubbs' metathesis catalysts. Early work had shown that ring closing metatheses mediated by the now widely-appreciated Grubbs type II catalyst **Qa** tended to proceed with superior reaction rates and overall conversions relative to **Qb**.[167] Delaude and co-workers subsequently found that for favorable substrates the benzimidazolylidene complex **Qc** could give *faster* initial rates for ring-closing metathesis than **Qa** (Figure 4.2).[168]

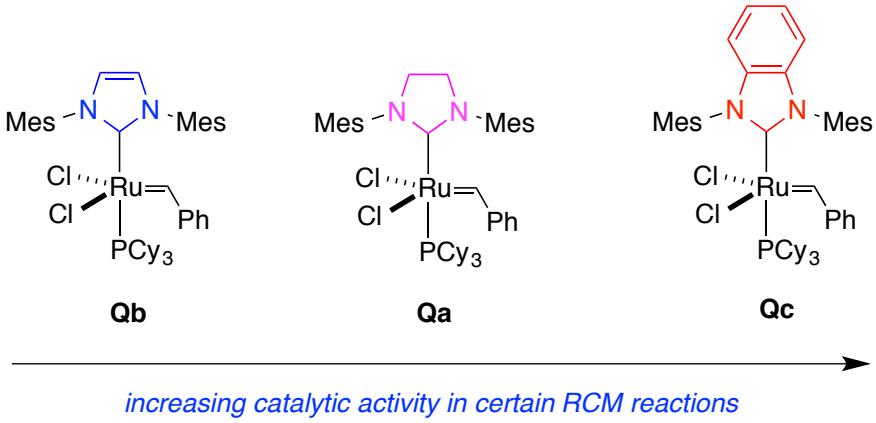
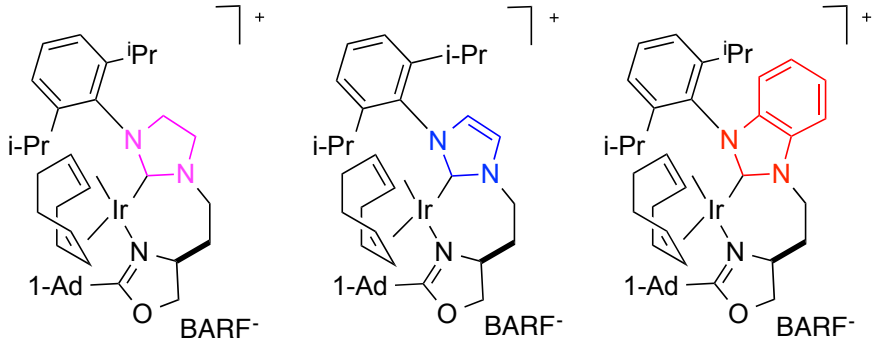


Figure 4.2. Comparing catalytic activity of Grubbs type II catalyst bearing imidazoline, **Qa**; imidazole, **Qb** and benzimidazole, **Qc** in certain RCM reactions.

In total, the considerations above indicate there is no reliable way to extrapolate free ligand properties in the series **a** – **c** to catalytic performance of complexes, and that even small stereoelectronic differences in the carbenes could have significant effects. Consequently, we were curious to test the series **1a** - **c** (Figure 4.3) that include our carbene catalyst **1b**. Complex **1b**, and similar chiral analogs of Crabtree's catalyst, are suitable for hydrogenation of trisubstituted alkenes without functional groups that typically coordinate to the metal in these complexes (CFGs).[16,17,169] Consequently, this study describes syntheses of the new complexes **1a** and **c**, and use of these to hydrogenate some largely unfunctionalized alkenes. Enantioselectivities were the critical end-point parameter that we wished to measure because the overriding application of **1b** is in asymmetric catalysts.



1a **1b** **1c**

Figure 4.3. Structure of catalyst **1** bearing different carbenes.

4.2 Results and discussion

To obtain catalyst **1a**, imidazoline **R** (Figure 4.4) was prepared via the known literature procedure.[170] Benzimidazole **S** (Figure 4.4), required for catalyst **1c**, is also a known compound,[171] but we synthesized it using a different method, *ie* reaction of the corresponding 1,2-benzenediamine with trimethyl orthoformate under acidic conditions, *p*-TsOH in this case. Removal of methanol from the reactions could promote the formation of product **S** in high yield.

R **S**

Figure 4.4. Structure of imidazoline **R** and benzimidazole **S**.

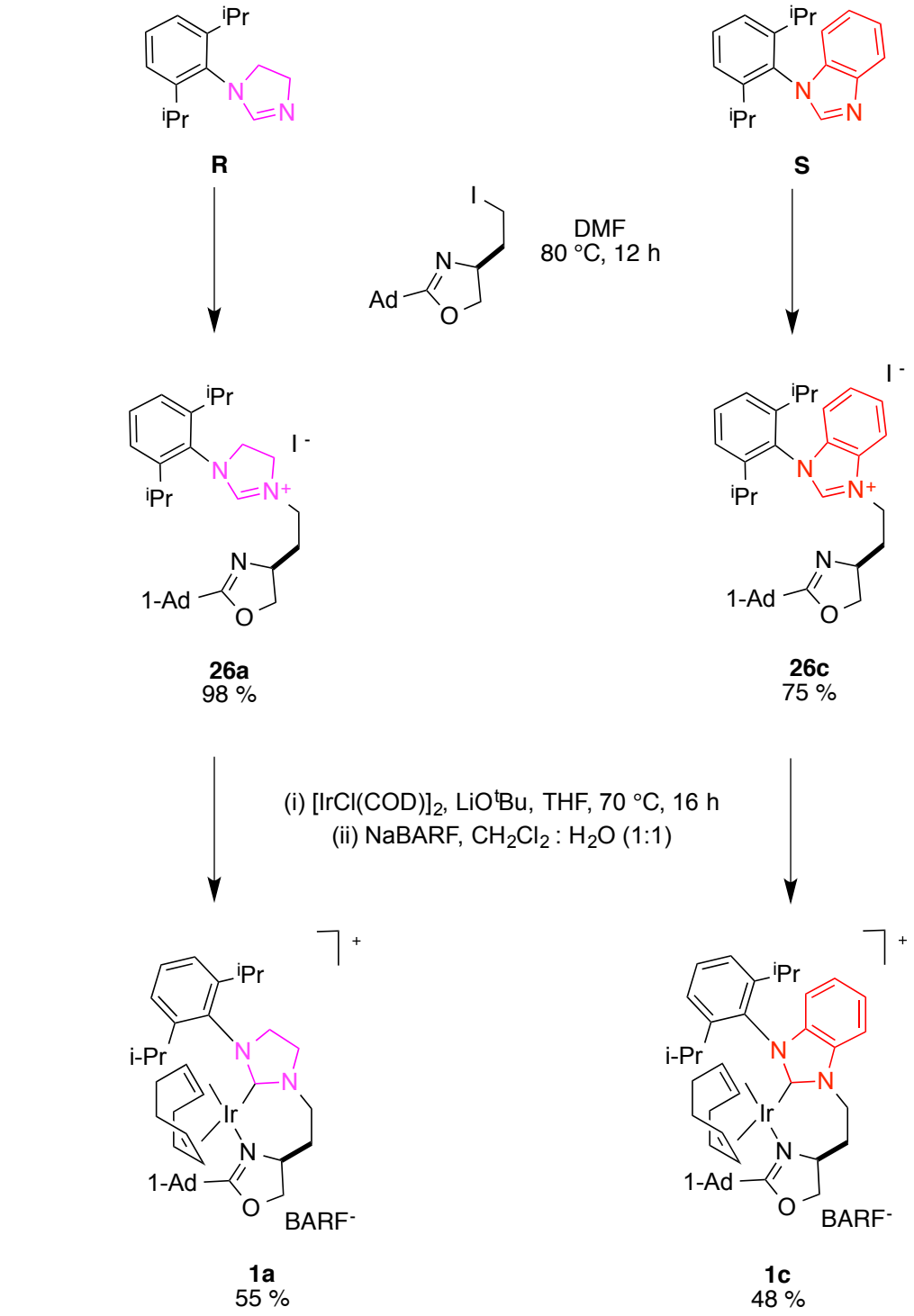
Both nucleophiles **R** and **S** were reacted with the appropriate iodo-oxazoline[30] in DMF to give the corresponding carbene precursors as shown in Scheme 4.1. Using identical conditions both carbene precursors were then deprotonated and reacted with $[Ir(COD)Cl]_2$ followed by anion exchange to obtain the final iridium complexes. Complex **1b** was prepared by following the known procedure developed in our group[30]

which can be scalable to obtain final complex around 5 grams. Comparison on physical properties showed that complex **1a** is yellow, whereas **1b** and **c** are orange and the solids are very identical. ^{13}C NMR chemical shifts of the coordinated carbene in this series **1a - c** are very similar: 178.4, 179.5, and 187.2 ppm, respectively.

Table 4.1 shows comparative data for a series of hydrogenations using catalysts **1a** – **c**. The stilbene derivative in entry 1 was included because it is the most widely studied substrate for asymmetric hydrogenations using chiral Crabtree's catalyst analogs.[16] The endocyclic alkene in entry 2 was chosen because that kind of substrates are not reduced with high stereoselectivities using catalyst **1b**. The other substrates shown in Table 4.1 are relevant to our studies on hydrogenations to form fragments of polyketide-derived natural products and other useful chirons.[33,132]

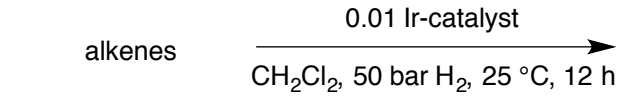
All the experiments summarized in Table 4.1 gave 100 % conversions under the conditions indicated. Stereoselectivities in these reactions were almost identical in almost every case; variation of the catalyst carbene feature had no significant effect.

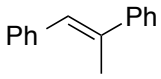
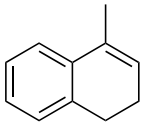
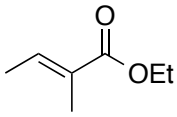
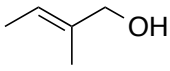
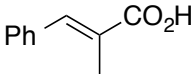
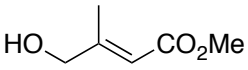
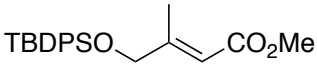
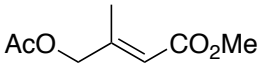
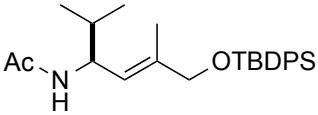
We have previously reported evidence that the carbene-containing catalyst **1b** is significantly less prone to generate protons in hydrogenation reactions than corresponding complexes that have phosphorus-based ligands in place of the carbene. [32] Calculations in that work indicated that the carbene complexes gave intermediates that are of the order of 10^7 times *less* acidic than similar *P*-containing complexes.[32] For the current study, similar calculations were undertaken for the series **1a** – **c**, and the data obtained are outlined in Table 4.2. Relative σ-donor and π-acceptor properties deduced from similar calculations are also shown. In the event, calculated pK_a values for the complexes are within a 2.2 unit range. Similarly, the calculated σ-donor and π-acceptor potentials for the free carbenes were within relatively tight ranges: ±0.2 and ±0.7 eV, respectively. These observations are consistent with Figure 4.5, which shows the HOMOs from these calculations are all relatively similar in shape.



Scheme 4.1. Syntheses of iridium catalyst **1a** and **c**.

Table 4.1. Stereoselective hydrogenations using the featured catalysts.

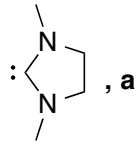
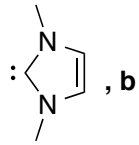
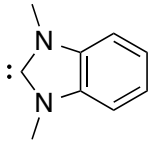


Entry		Stereoselectivity[a]		
		1a	**1b**	**1c**
1		93	99	95
2		12	5	15
3		57	63	55
4		77	83	75
5		70	65	66
6		93	96	95
7		91	93	93
8		94	95	94
9 [b, c]	 *syn:anti*	49:1.0	49:1.0	48:1.0

[a] Enantioselectivity unless it stated. [b] Diastereoselectivity.
[c] Reactions using 2 mol % of **1a – c**.

Experimental validation of the calculated pK_a trends discussed above was obtained by hydrogenation of 1,2-diphenylpropene using **1a** – **c** as shown in Figure 4.6, then adding a pH indicator. Whereas, we have shown previously that *N,P*-complexes tend to give red solutions (similar to the control in Figure 4.6a),[32] all three complexes **1a** – **c** gave light yellow solutions indicating the reaction medium is not acidic.

Table 4.2. σ-Donors, π-acceptor and pK_a of intermediate in hydrogenation reaction of complexes **1a** – **c**.

	σ-donor (eV)	π-acceptor (eV)	pK_a complex **1**
 , **a**	-4.690	-0.119	18.0
 , **b**	-4.865	0.063	17.4
 , **c**	-5.080	-1.337	15.8

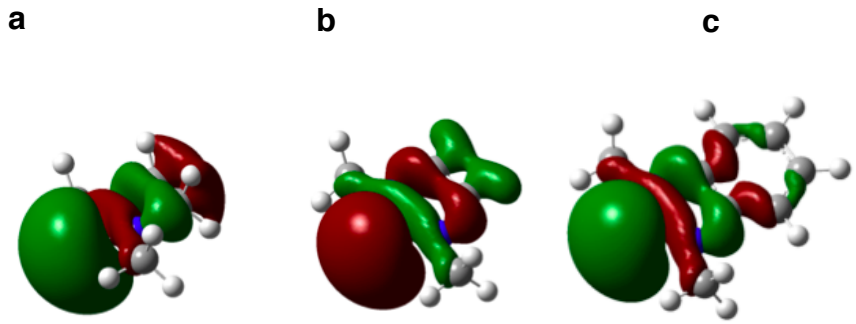


Figure 4.5. HOMO of carbene electron from imidazoline, **a**; imidazole, **b** and benzimidazole, **c**.

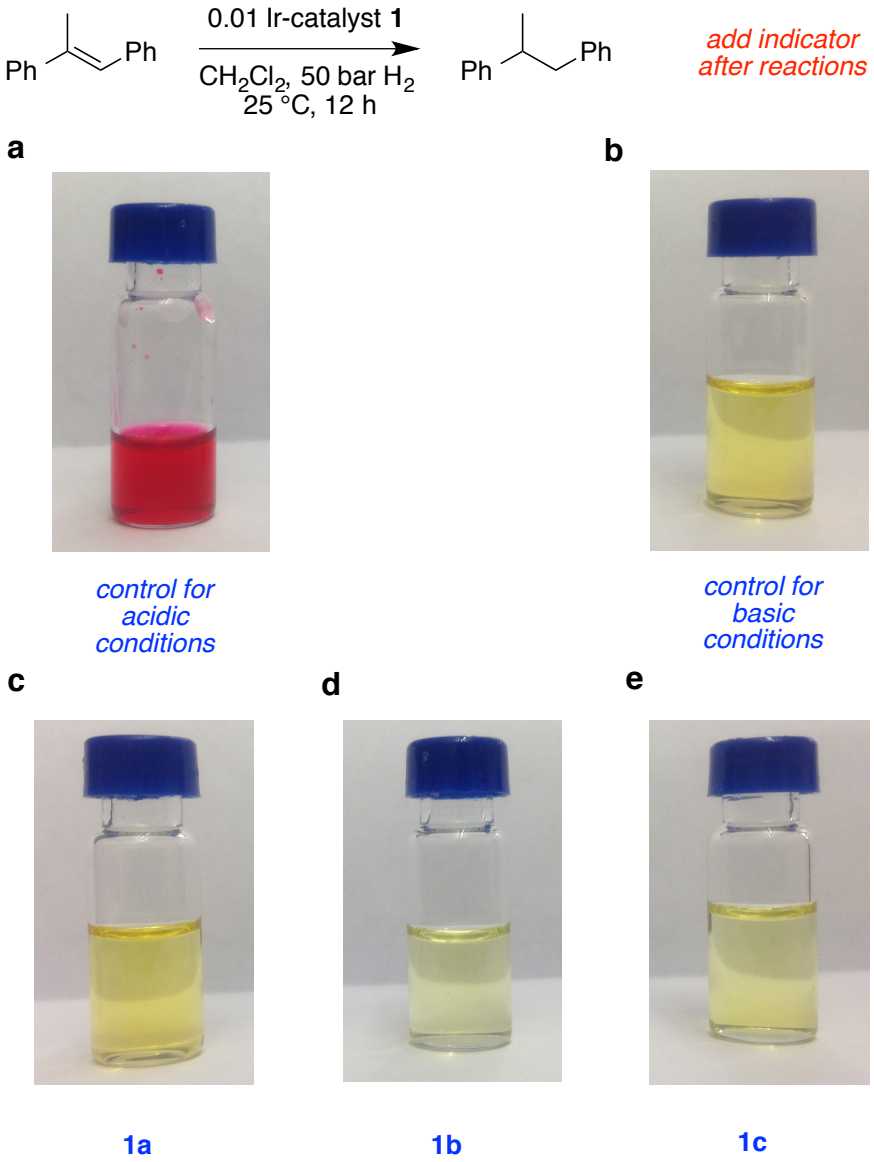
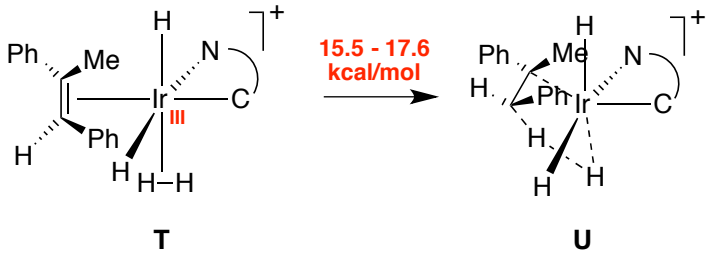


Figure 4.6. Hydrogenation with catalyst **1**: **a** methyl red with acetic acid in CH_2Cl_2 (control for acid); **b** methyl red with Et_3N in CH_2Cl_2 (control for base); **c** catalyst **1a** with methyl red; **d** catalyst **1b** with methyl red; and **e** catalyst **1c** with methyl red.

Our hypothesis regarding the mechanism of hydrogenation with **1b**, based on calculations, indicated[35] a strong *trans*-effect orients the alkene ligand opposite to the carbene in intermediate **T** as indicated in Figure 4.7. These calculations also indicate transformation of **T** into the transition state **U** was predicted to be the rate-limiting step in the catalytic cycle. We propose all the carbene ligands (abbreviated to C in Figure 4.7) maintain that strong *trans*-effect in the catalysis, and there are insufficient steric differences to perturb the enantioselectivities.



T **U**

Figure 4.7. Transformation of **T** to **U** is predicted to be rate-limiting in the catalytic hydrogenation of *trans*-1,2-diphenylpropene mediated by complex **1b**.

In order to explain the relatively poor performance for catalyst **1b** with endocyclic substrates, as in entry 2 of Table 4.1, calculations were performed corresponding to use of catalyst **1b** in entry 1, as reported previously, involved evaluating the energies of three species. Specifically these were: (i) the intermediate **T** in Figure 4.7 before the turnover limiting step; (ii) the transition state that relates **T** and **U**; and, (iii) the energy of the intermediate **U** after the turnover limiting step. These studies proved that the energy of that intermediate **U** is closely related to the transition state energy.[35] Those studies also showed four pathways should be considered. These are two for each enantio-face of the alkene, and, for each enantio-face, pathways corresponding to two different π-complex rotamers related by 180° rotation around the metal to π-bond in the starting intermediates **T**. These correspond to putting each of the two inequivalent phenyl groups of the complexed alkene between the smaller pocket between the bulky 2,6-di-*iso*-propylphenyl and adamantly substituents. The conclusion from this study is that the pathway from intermediate **T** to **U** (based on the relative

energies of these two intermediates) for hydrogenation of the alkene in Table 4.1, entry 1, to give the (*S*)-product was 5.91 kcal/mol more stable than any of the two pathways leading to the (*R*)-enantiomer.

In the current study, calculations were preformed using exactly the same procedures as before to assess the energies of the same four types of pathways for the endocyclic substrate in entry 2. Figure 4.8 shows the two of the four key intermediates (analogous to **U**), and their relative energy differences from the starting p-complexes (analogous to **T**); all the values are normalized relative to the most favorable pathway identified. That most favorable pathway corresponds to production of the (*R*)-enantiomer, but there is another calculated to be only 0.21 kcal/mol higher in energy that leads to the (*S*)-enantiomer. Thus these calculations explain the poor enantioselectivities for endocyclic alkenes: in both intermediates shown the edge-fused ring system stacks above the $(^{i}Pr)_2C_6H_3$ ligand aryl substituent.

4.3 Conclusions

New hydrogenation catalysts **1a** and **c** were synthesized to compare the electronic effect of *N*-heterocyclic carbenes for asymmetric hydrogenation. We cannot rule out the possibility that differences will emerge for these catalytic reactions mediated by complexes **1a** – **c**, especially from stereoselectivity. However, the current study demonstrates there are negligible differences between them in the asymmetric hydrogenation reactions shown in Table 4.1. Although the catalysts gave good performance in many substrates, poor enantioselectivities in the hydrogenations of endocyclic substrates seem to arise because hydrogenation pathways for the two enantiofaces of this substrate proceed through energetically similar turn-over limiting steps as illustrated in Figure 4.8.

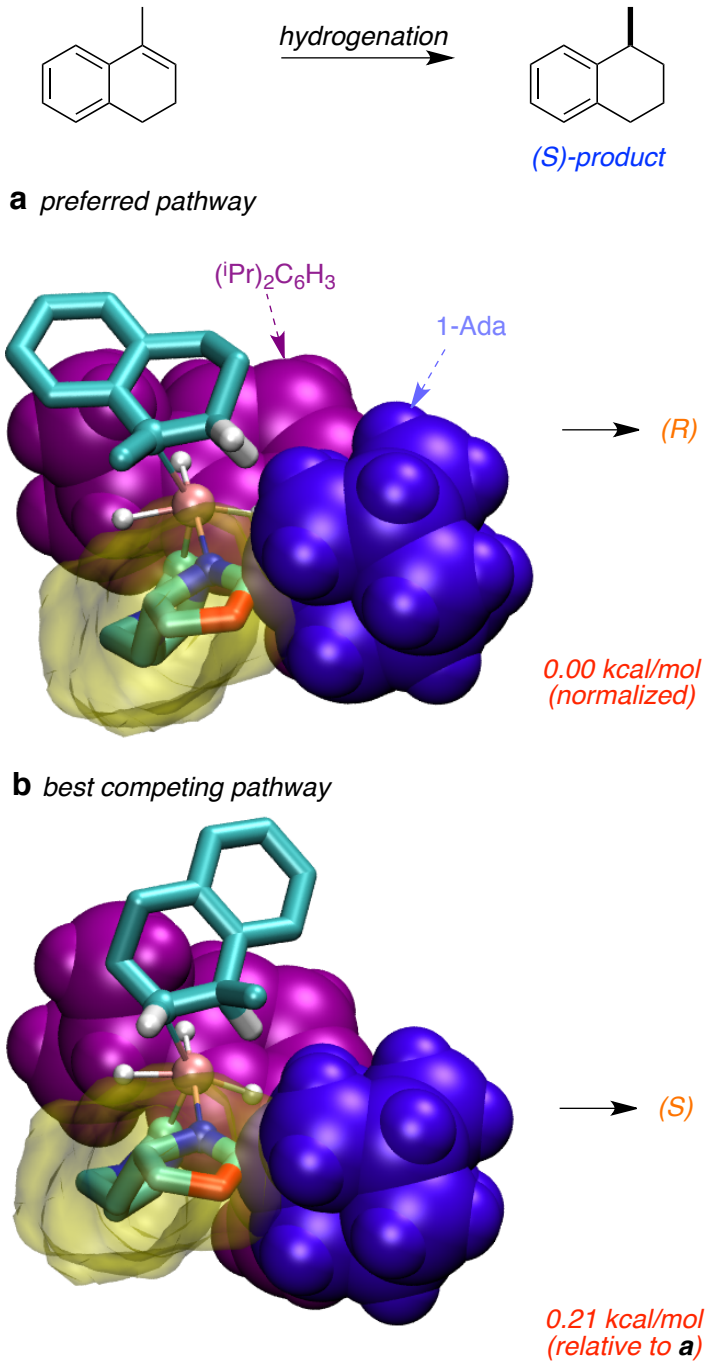


Figure 4.8. Intermediates in two most preferred pathways for hydrogenation of endocyclic substrate lead to different enantiomers have the same energies (within error limits for these calculations).

CHAPTER V
METATHESIS FOR CATALYST DESIGN: METACATALYSIS

5.1 Introduction

During the past two decades, several chiral phosphorus compounds especially phosphines and phosphites were synthesized for many catalytic reactions as homogeneous and heterogeneous ligands. To get effective catalysts with high stereoselectivities, ligands need suitable designs with high experience. Moreover, influence of temperature, pressure, time, solvents and additives have to be evaluated until the best condition was discovered. Less flexible ligands, such as bidentate or tridentate chelations are even harder to design and sometimes lead to very large library of ligands with many different substitutent combination. All of these are time consuming that could lead to unpredictable results.

In situ catalyst formation by mixing *monodentate* ligands with a reactive metal salt or complex (Figure 5.1) has been used extensively for rapid identification of superior catalysts by Reetz,[172-175] Feringa/Vries,[176-179] and by others.[180-183] Those groundbreaking studies lead to several conclusions that were not appreciated before this approach was conceived. First, even though it was known that high enantioselectivities could be obtained using certain *monodentate* ligands,[184] formation of dynamic combinatorial mixtures of complexes in this way has proved to be an exceptionally efficient catalyst optimization strategy. Second, mixtures of two ligands sometimes give higher enantioselectivities than experiments in which two equivalents of either of the two pure ligands are used. Third, there are situations in which superior enantioselection has been achieved when one of the monodentate ligands is *achiral*. Fourth, time has shown that this approach is reasonably general, having been widely applied to asymmetric hydrogenations of alkenes with coordinating functional groups (CFGs),[172-179] and to 1,4-additions to electron-deficient alkenes,[185-188] allylic substitution,[189-191] hydrovinylation,[192,193] and cross coupling.[194]

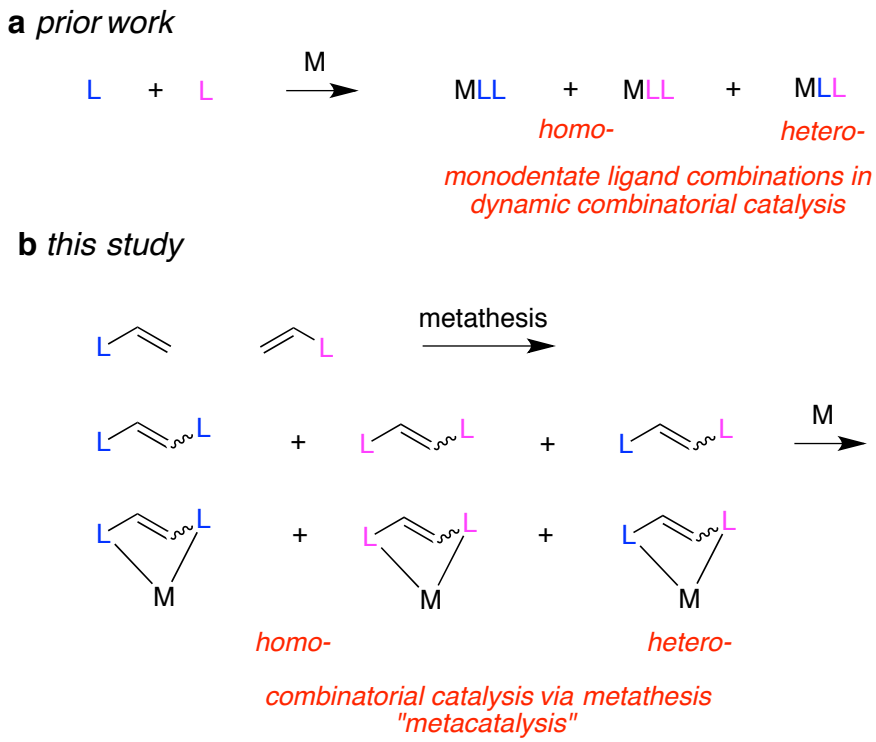


Figure 5.1. **a** Dynamic combinatorial catalysis is known; but, **b** can bidentate ligands be similarly formed via metathesis?

In reality, mixtures in dynamic combinatorial catalysis usually are significantly more complicated than Figure 5.1a suggests. For instance, it is possible that active complexes with one or three ligands might be involved. Moreover, Hartwig has shown that ostensibly monodentate ligands in some reactions are, in fact, bidentate as a result of metalation processes.[195-198] In short, dynamic combinatorial catalysis trades some control of the mixtures being screened for the ability to make potential catalysts quickly.

Efficiency is possible in dynamic combinatorial catalysis by generating different combinations of monodentate ligands. However, it would be highly desirable to produce *bidentate* ligands instead, without significantly compromising the efficiency. This is because appropriately designed bidentate, chelating ligands have several attributes conducive to the design of stereoselective catalysts, mostly related to the fact that their complexes exist in fewer accessible low energy conformers. A superior bidentate ligand may exist corresponding to each effective combination of monodentate ligands

identified in dynamic combinatorial chemistry; in practice the problem is finding this ligand.

Research described in this manuscript was undertaken to obtain proof-of-principle for the concept illustrated in Figure 5.1b. We envisaged olefin metathesis[199] could be used to convert alkene-containing ligands with one *P*-center into mixtures of compounds with two. In simple cases in which only the *P*-centers coordinate to the metal, this represents conversion of monodentate ligands to bidentate ones; metathesis to form catalysts is referred here as *metacatalysis*. Thus, if the metathesis reactions are efficient enough that purification of the ligands before the test reaction is unnecessary, then metacatalysis could be almost as convenient as dynamic combinatorial processes featuring monodentate ligands, but have the distinction that bidentate "catalyst space" is covered.

5.2 Results and discussion

5.2.1 Selection of the metathesis substrates and test reactions

Several considerations guided selection of the alkene chirons that were used as metathesis substrates in this work. First, the alkenes should be conveniently assembled from commercial starting materials. Second, carbene intermediates in the catalytic cycle should *not* permit a stable 5-ring chelate to be formed since this would tend to depress the catalytic activity.[200] The third consideration follows because the previous one tends to impose design constraints that favor large-ring chelates, and because these would predominantly feature *E*-alkenes (assuming standard metathesis catalysts were used). Thus it was desirable to use monomers for which the anticipated macrocyclic chelates would be formed from large fragments; our hypothesis was that this would tend to decrease the number of accessible conformational states as a result of steric packing effects. Finally, it was necessary to avoid situations in which the corresponding combinations of monodentate ligands for the featured catalytic reaction already gave high stereoselectivity. In other words, the objective of this study was to see if

metacatalysis could give improved enantioselectivities, so it was logical to choose situations that allowed for substantial improvement.

Based on the considerations outlined above, we elected to work with *pseudo*-enantiomeric phosphite derivatives of quinidine and quinine, **27** and **28** respectively (Figure 5.2). One monodentate ligand of this kind, **27e** where $(RO)_2$ = 1,2-diphenyl-1,2-ethylenedioxy, has been reported previously and used for Pd-mediated allylation reactions; enantioselectivities up to 88% were obtained.[201] In the event, ligands **27a** – **h** and **28g** – **h** were prepared in one-pot reactions and isolated in yields ranging from 30 - 85 % after flash chromatography.

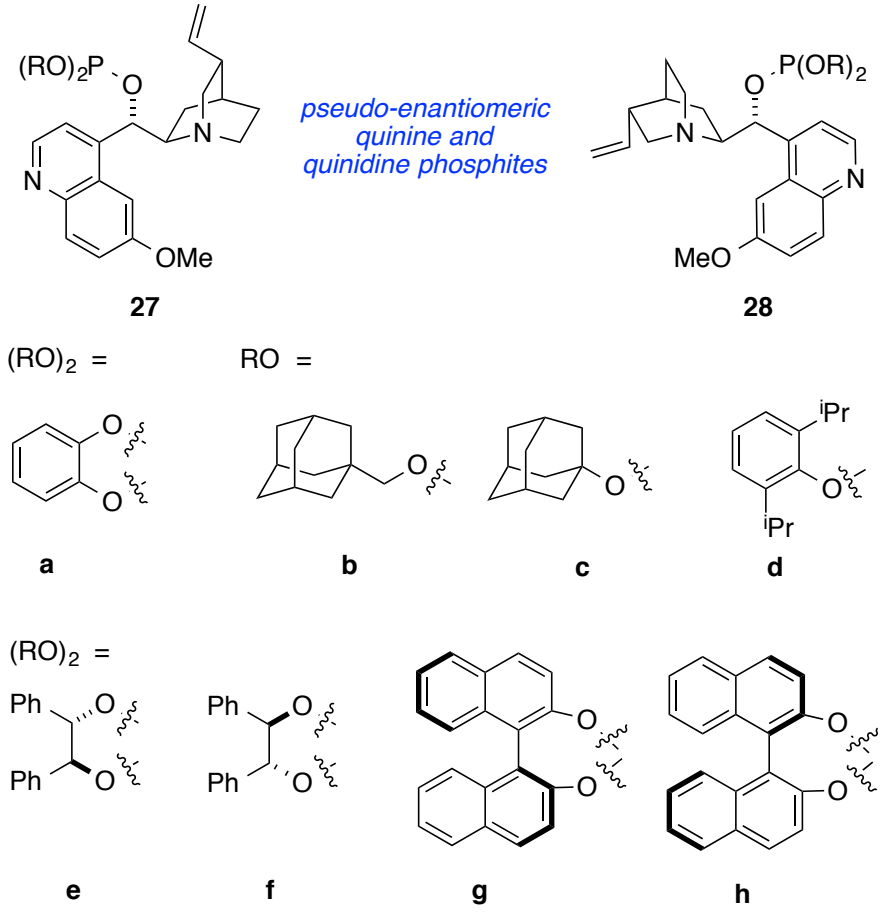


Figure 5.2. Alkene-phosphite chirons featured in this work. Ultimately, the study focused on **27g** – **h**, and **28g** – **h**.

Hydrogenations of largely unfunctionalized alkenes were selected as the test reactions, for the following reasons. Some of the most successful catalysts in these processes are iridium complexes with *N,P*-ligands;[16,17,169] chirons **27** and **28** have the potential to use *P*- and *N*-atoms to coordinate in this way (Figure 5.3). Consequently, the archetypical hydrogenation of this kind was used to triage some of the monomers (reaction 5.1). On the basis of the data shown, only the 2,2'-binaphthol-based ligands **g** and **h** were selected for further studies.

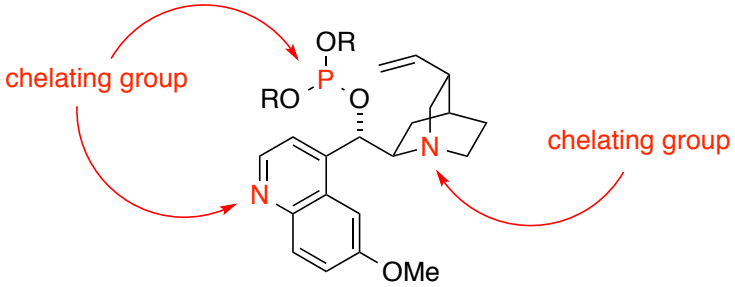
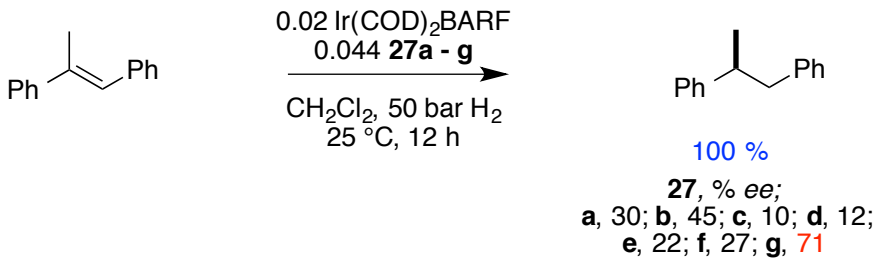


Figure 5.3. Chelating group in structure of cinchona alkaloids phosphite derivatives.



reaction 5.1

5.2.2 Metathesis of the alkene monomers

Alkene metatheses of substrates **27** and **28**, **g** and **h**, were studied as a prelude to the featured catalytic reactions. It was not obvious that these metatheses reactions would proceed with high conversions because even monosubstituted alkenes tend to react slowly if the allylic site is bulky.[202] Moreover, the alkenes featured here also contain phosphite centers that could similarly retard the catalysis. Throughout, we restricted our studies to the more convenient Ru-based metathesis catalysts; the related Mo-centered catalysts were not explored.

In the event, the Grubbs-Hoveyda second generation system **V** gave good conversion of the monomers to the disubstituted alkenes **27' – 27'** and **28' – 28'** (Figure 5.4). This transformation was monitored by loss of the methylene ^{1}H and ^{13}C NMR signals while the vinylic C<u>H</u> shifted to the product resonance. Only one vinylic C<u>H</u> NMR signal was observed in each case indicates that only the E-isomer of the alkene was formed in detectable amounts. The ^{31}P NMR resonances of the products were within 0.5 ppm ($CDCl_3$) of the starting materials.

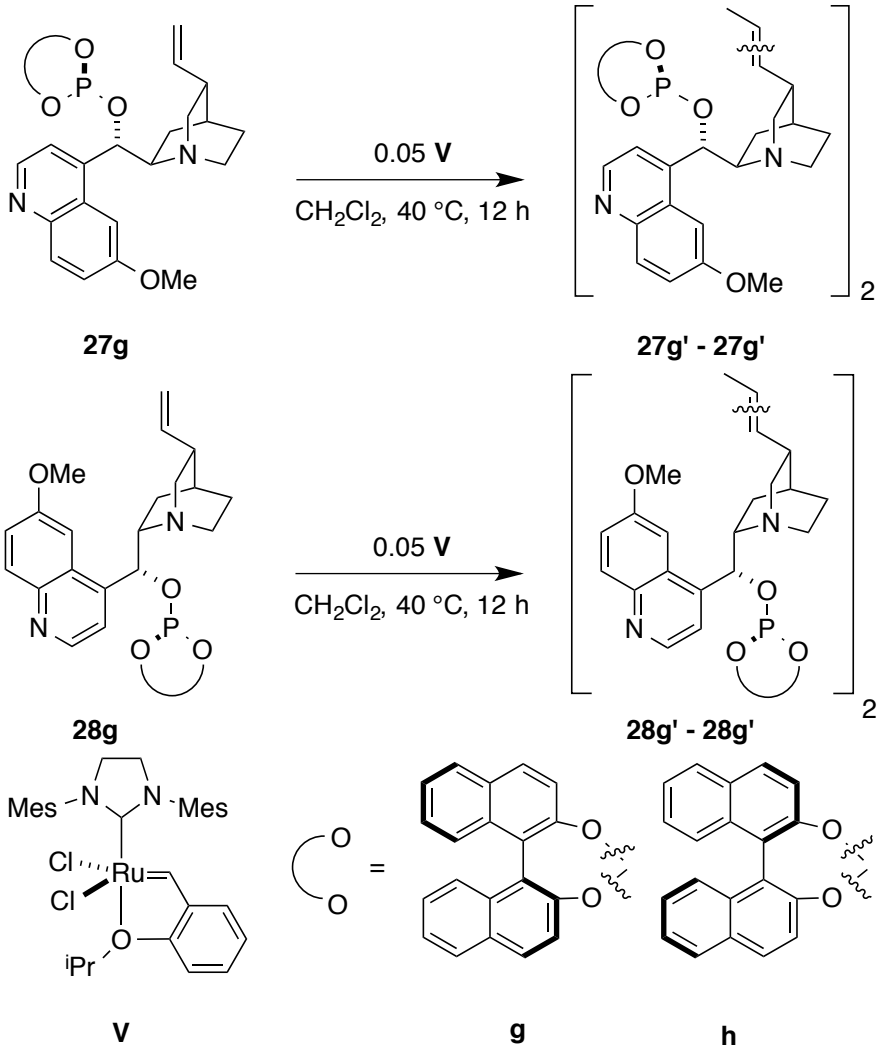


Figure 5.4. Alkene-phosphite chirons **27g** – **h**, and **28g** – **h**, could be joined via alkene metathesis.

Test reactions performed using mixtures of ligands **27** and **28** gave mixtures with complicated ^{1}H and ^{13}C NMR spectra. ^{31}P NMR signals of the products in the crude reaction mixtures could not be resolved, and we were unable to separate the components of the mixture using either normal or reverse phase HPLC because they all had very similar polarities. In retrospect it is clear that the polarity of products in these metathesis reactions are dominated by the amine-alkaloid parts; adding different hydrophobic fragments to the phosphite does not impart differences that are large enough even to see the isomers by analytical HPLC.

5.2.3 Crude metathesis reactions do not give viable hydrogenation catalysts

There have been reports of hydrogenation reactions mediated by Ru-based complexes for metathesis.[203] However, these processes did not feature trisubstituted alkenes without coordinating functional groups (CFGs) for which exceptional hydrogenation catalysts are required,[16] so it was necessary to test if complexes like **V** could mediate hydrogenation. In the event, most of alkenes in these projects were tested hydrogenation mediate by **V**. The results indicated that in some substrates (Figure 5.5 and 5.7), catalyst **V** did not hydrogenate the alkenes. The same catalyst, however, did hydrogenate some of trisubstituted contains coordinating functional group (Figure 5.6 and 5.8) giving only <2 % of products under the condition indicated.

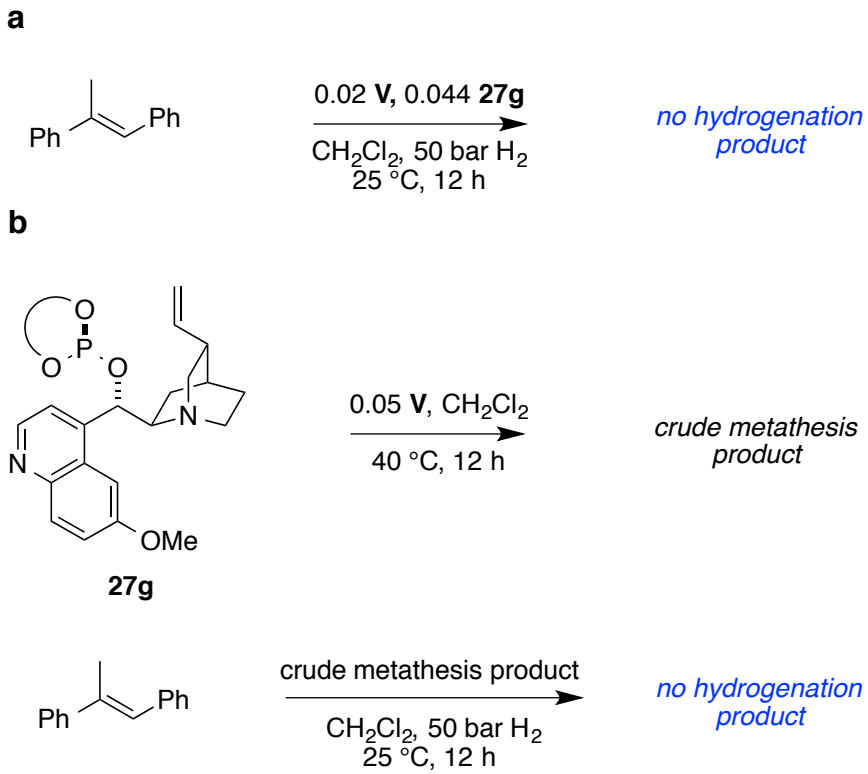


Figure 5.5. **a** Catalyst **V** did not mediate hydrogenation of *E*-1,2-diphenylpropene under the conditions shown. **b** Catalyst **V** was used to mediate metathesis, then hydrogen and a trisubstituted alkene were introduced; the latter was not hydrogenated.

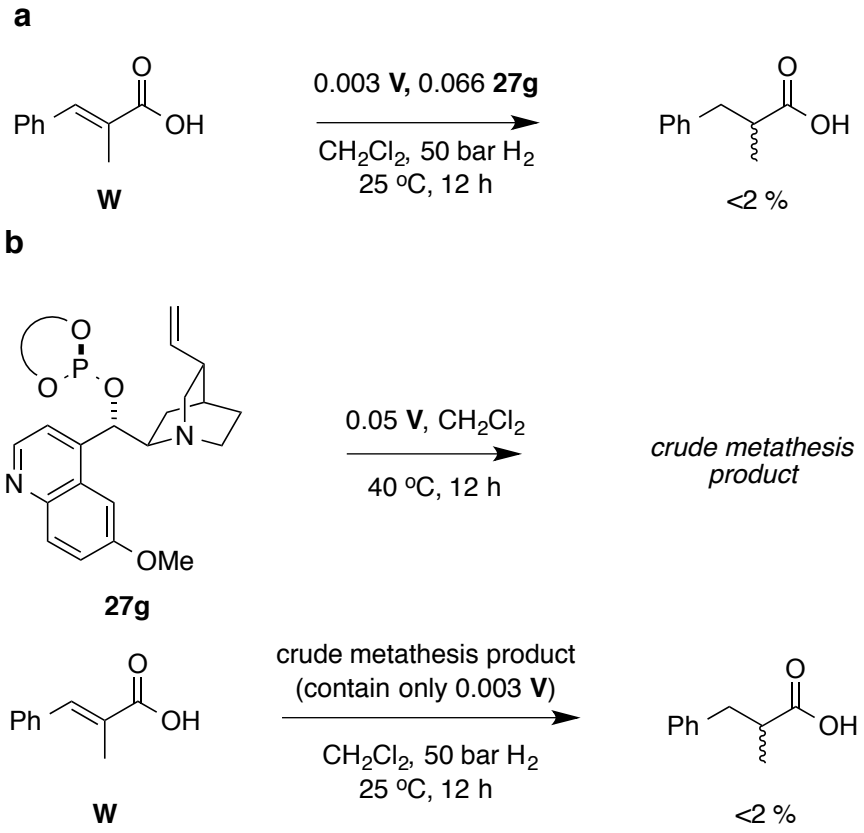


Figure 5.6. **a** Catalyst **V** gave less than 2 % of product from hydrogenation of α-cinnamic acid **W** under the conditions shown. **b** Catalyst **V** was used to mediate metathesis, then hydrogen and a trisubstituted alkene were introduced; the latter was hydrogenated with less than 2 %.

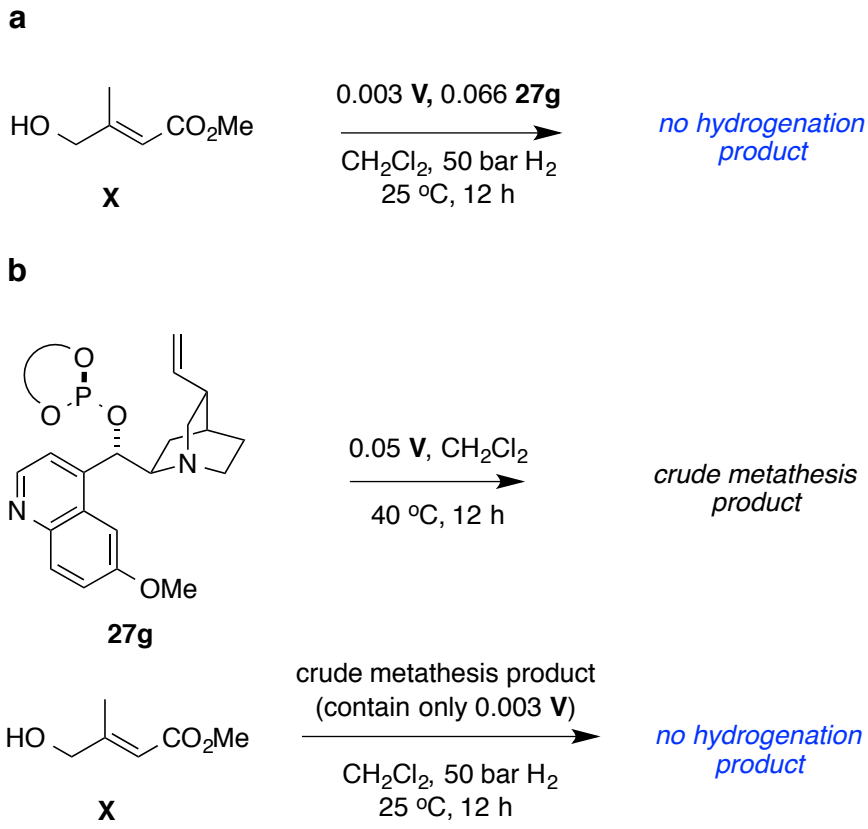


Figure 5.7. **a** Catalyst **V** did not mediate hydrogenation of hydroxy-ester **X** under the conditions shown. **b** Catalyst **V** was used to mediate metathesis, then hydrogen and a trisubstituted alkene were introduced; the latter was not hydrogenated.

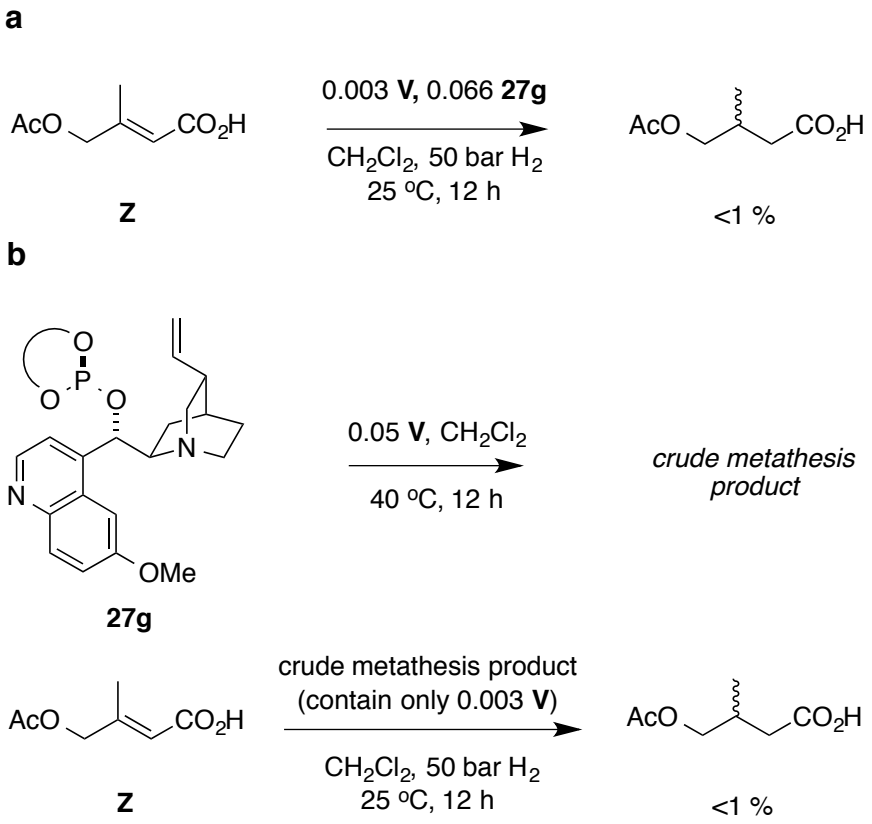


Figure 5.8. **a** Catalyst **V** gave less than 1 % of product from hydrogenation of acetoxy-acid **Z** under the conditions shown. **b** Catalyst **V** was used to mediate metathesis, then hydrogen and a trisubstituted alkene were introduced; the latter was hydrogenated with less than 1 %.

5.2.4 Hydrogenations of cinnamic acids derivatives with monodentate ligands

Hydrogenations of α,β-unsaturated acids and esters (see below) can be used to make chirons for polyketide-derived natural products and other materials,[33,90] but these reactions with simple substrates are difficult to perform with high enantioselectivities.[11] Consequently we decided to test combinations of our ligands in these reactions, beginning with a substrate that is relatively easy to hydrogenate with significant enantioselectivity, α-methylcinnamic acid **W**.

The first step in probing the featured hydrogenation reactions was to establish "baseline data" representing enantioselectivities obtained using the monodentate ligands, *ie* precursors to the fragments to be connected via metathesis. Figure 5.9 showed that catalysts formed *in situ* from $Ir(COD)_2$ BARF and ligand **27g** in a ratio of approximately 1:2 gave complete conversion to product with an *ee* of 60 %.

At this stage we choose to check the effects of adding an achiral ligand. Figure 5.9 (right side) shows data for the experiment in which the reaction described above was repeated using a mixture of $Ir(COD)_2$ BARF, **27g**, and PPh_3 in a ratio of approximately 1:2:1 complete conversion and 64 % *ee* was observed. On the basis of these observations, no more tests were performed with the achiral PPh_3 additive because no significant enhancement in *ee* was obtained when it was added. Curiously, when the same reaction was run using a ~1:1:1 ratio of $Ir(COD)_2$ BARF, **27g**, and PPh_3 the product was again formed exclusively, but it was racemic (Figure 5.9, center); this observation gave more support to the decision not to investigate PPh_3 as an additive more extensively.

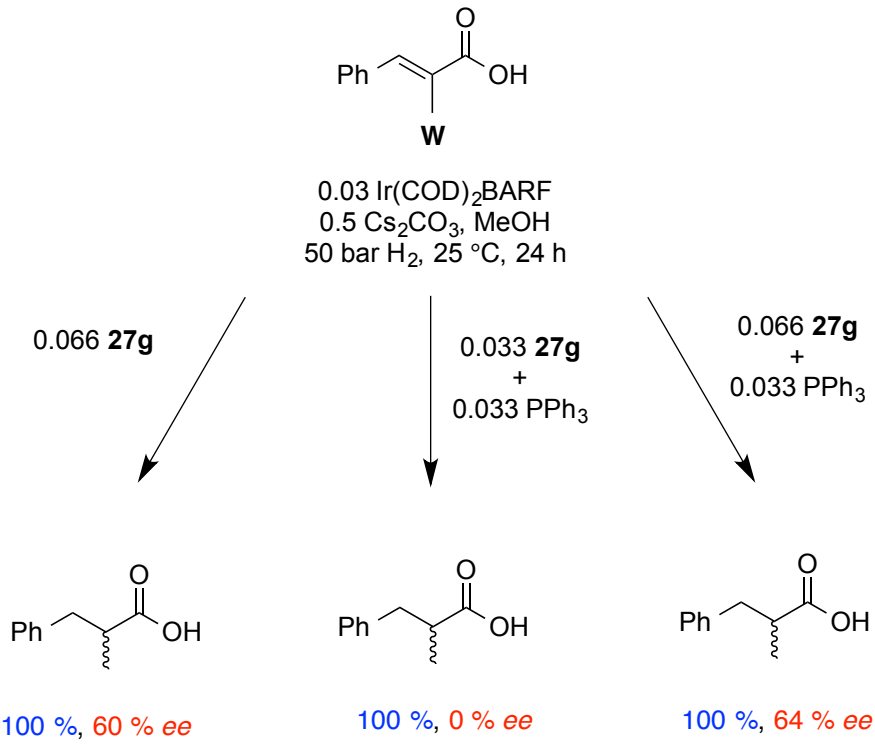
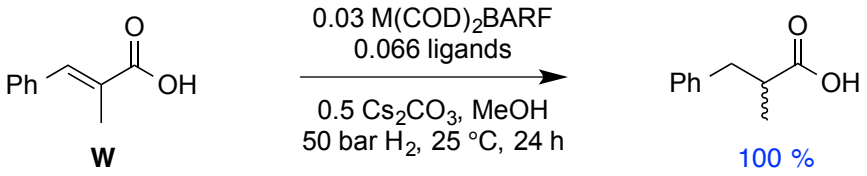


Figure 5.9. Hydrogenation of α-methylcinnamic acid **W** using catalysts formed from **27g** with and without PPh_3.

Another series of experiments was performed to compare rhodium- and iridium-based catalyst precursors in reactions using mixtures of the monodentate ligands **27g**, **27h**, **28g**, and **28h**; these data are shown in Figure 5.10. Throughout, 100 % conversion to the product was obtained under the conditions indicated. The data in Figure 6 clearly shows that the iridium complexes featured in part **a** generally gave superior enantioselectivities when compared to their rhodium analogs (**b**). For the Ir-data in part **a**, all the homo-combinations gave superior enantioselectivities than the heterocombinations (*eg* experiments with ~2 equivalents of ligand **27g**, and with ~2 equivalents of ligand **27h**, both gave better enantioselectivities than when **27g** and **27h** were used together in a 1:1 ratio; top of part **a**). In the Rh-series (part **b**) there are heterocombinations that proved to be more enantioselective than one of the homo-combinations, but never both.



a M = Ir

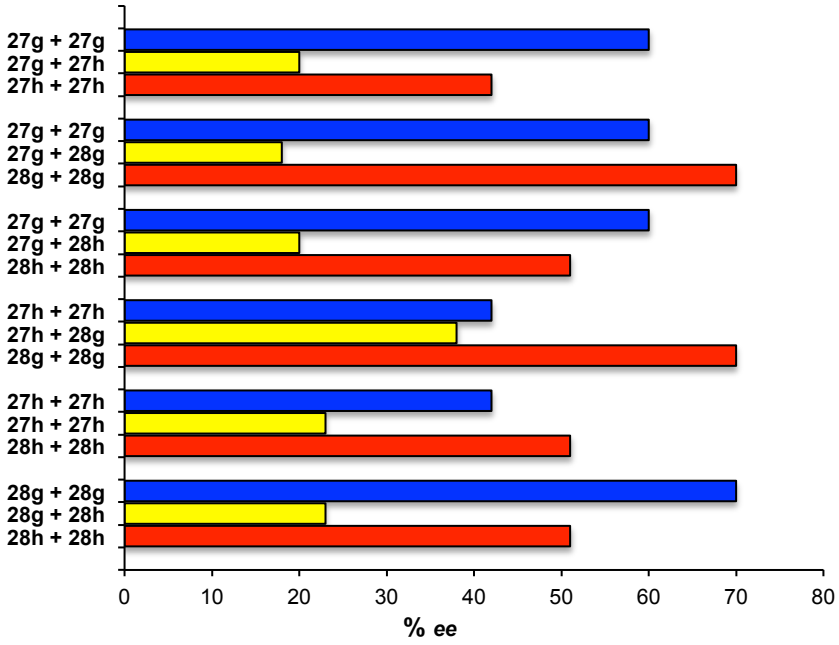


Figure 5.10. Hydrogenation of α-methylcinnamic acid **W** using catalysts formed from the monodentate ligands **27g**, **27h**, **28g**, and **28h** with: **a** $Ir(COD)_2^+$; and, **b** $Rh(COD)_2^+$.

b M = Rh

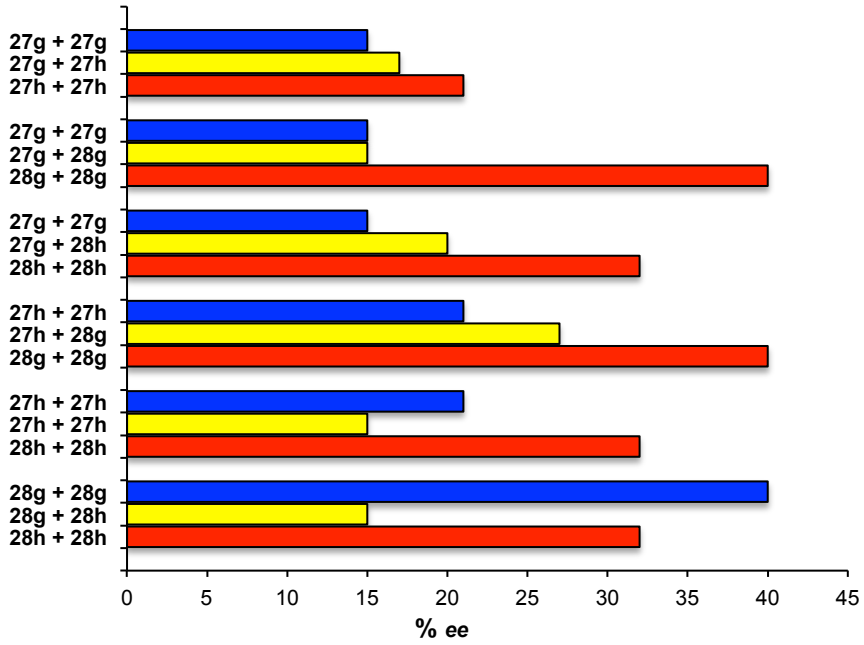


Figure 5.10. Continued.

5.2.5 Hydrogenations of α,β-unsaturated ester derivatives with monodentate ligands

From the perspective of potential users, reduction of α-methylcinnamic acid **W** is probably less interesting than the corresponding reactions of α,ω-functionalized substrates like the alcohol **X** shown in Figure 5.11a, or the acetate **Y** shown in Figure 5.11b. Data were collected only for the Ir-based complexes because such catalysts tend to be more suitable for this type of substrate (*ie* where the catalyst can be ligated by *N*,*P*-ligands and the substrate has functional groups that are only weakly coordinating),[11] and because Ir-based complexes were superior to the Rh-based ones for substrate **W**.

For alcohol **X**, Figure 5.11a shows that homocombinations of ligand **27g** (blue bars) gave the best enantioselectivities. Just as in Figure 5.10, enantioselectivities for some heterocombinations (yellow bars) are superior to one homocombination, but there was no heterocombination that was superior to both the corresponding homocombinations.

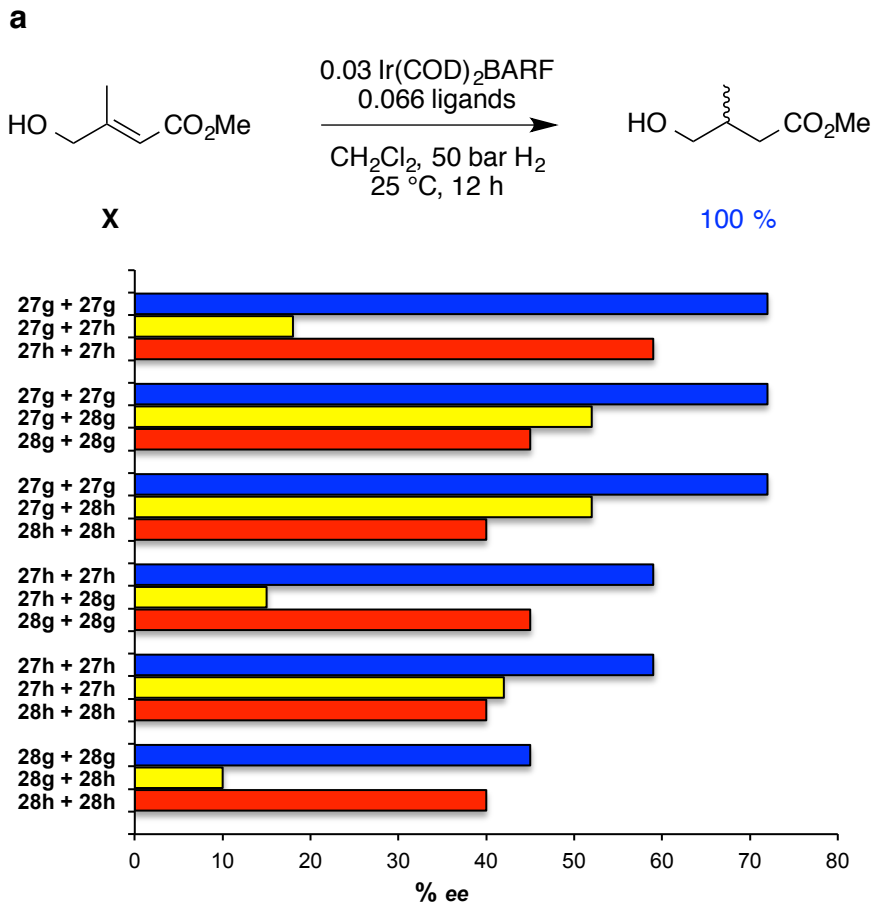


Figure 5.11. Hydrogenation of: **a** hydroxyester **X**; and **b** acetoxyester **Y** using catalysts formed from the monodentate ligands **27g**, **27h**, **28g**, and **28h** with: $Ir(COD)_2^+$.

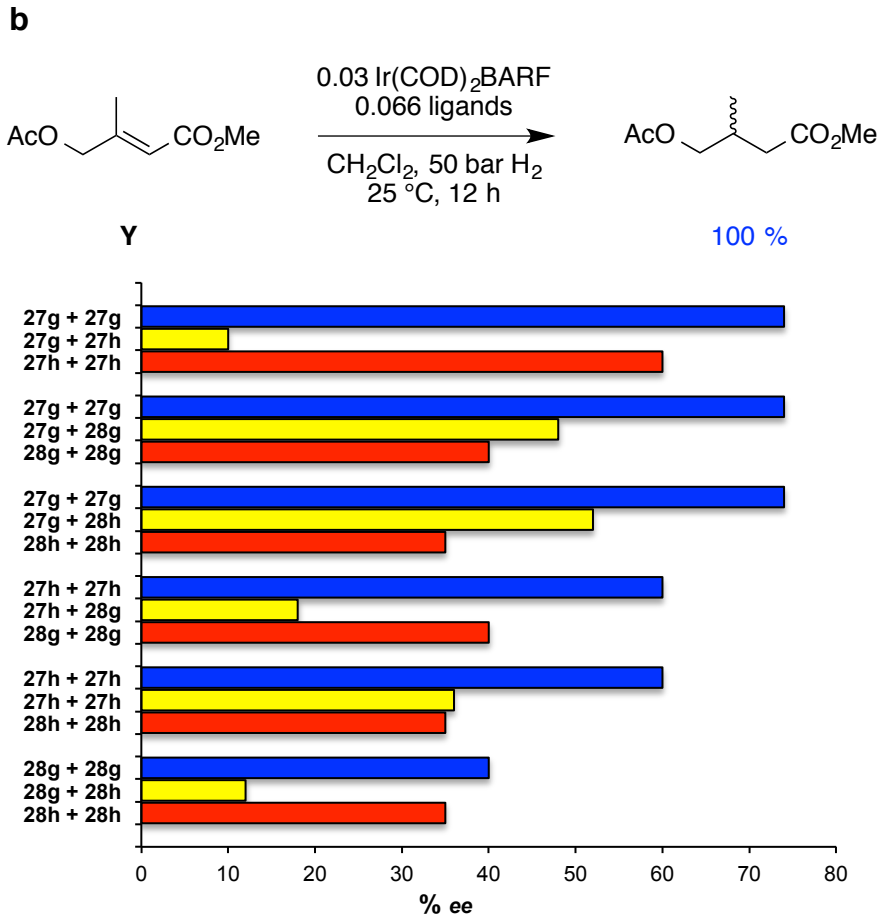


Figure 5.11. continued.

5.2.6 Hydrogenations of α,β-unsaturated ester derivatives with bidentate ligands formed via metathesis

Having established enantioselectivities for the hydroxyester **X** and the acetoxyester **Y** using monodentate ligands, we then used metathesis to form bivalent ligands from the same quinidine- and quinine-based phosphites *in situ* and tested these. For example, in Figure 5.11, **27g** + **27h** refers to the combination of monodentate ligands, whereas in Figure 5.12, where these same monodentate ligands are subjected to metathesis as in Figure 5.4, **27g' - 27h'** refers to that heterocombination (which contains two homodimers and one heterodimer; see above). The bars in Figure 5.12 show the *enantioselectivity differences obtained relative to the corresponding hydrogenations*

with the corresponding combinations of monodentate ligands; positive values indicate the dimer combinations gave superior enantioselectivities. Throughout, the sense of the enantioselection is governed by the binaphthyl chirality, series **g** gives the *S*-enantiomer while the *R*-enantiomer is consistently formed from the **h** series. Enantioselectivity values (as opposed to differences) are indicated by the numbers on the bars themselves. Thus an improvement of up to 37 % *ee* was observed under the *metacatalysis* for the hydroxyester **X** (Figure 5.12a), and up to 34 % for the acetoxyester (5.12b). Interestingly, the *same* metacatalysis combination, **27h' – 28g'**, gave the maximum improvement for the hydroxyester **X** and the acetoxyester **Y**. However, the overall best selectivities for these reactions were in the monomer combination series (**27g** + **27g** in Figure 5.11a and b) and not for the dimers formed via metacatalysis.

Finally, we decided to test one of the carboxylic acid substrates that correspond to one of Figure 5.12. For these experiments the acetoxy acid **Z** was selected because acetates gave marginally higher enantiosectivities than the alcohols for the esters in Figure 5.11 with monodentate ligands. Data for hydrogenation of the acetoxy acid **Z** (Figure 5.13) show a maximum improvement of 32 % *ee* (for **28g' – 28g'**). The best overall selectivity for the carboxylic acid hydrogenations in Figure 5.11 is for **28g** + **28g** and **28g' – 28g'**, *ie* the same combination in the monomer (**a**) and dimer (**b**) series. The optimal enantioselectivity was superior for the dimers (**b**) from metacatalysis relative to the monomers (**a**) (92 *vs* 60 % *ee* for the combinations involving **28g**).

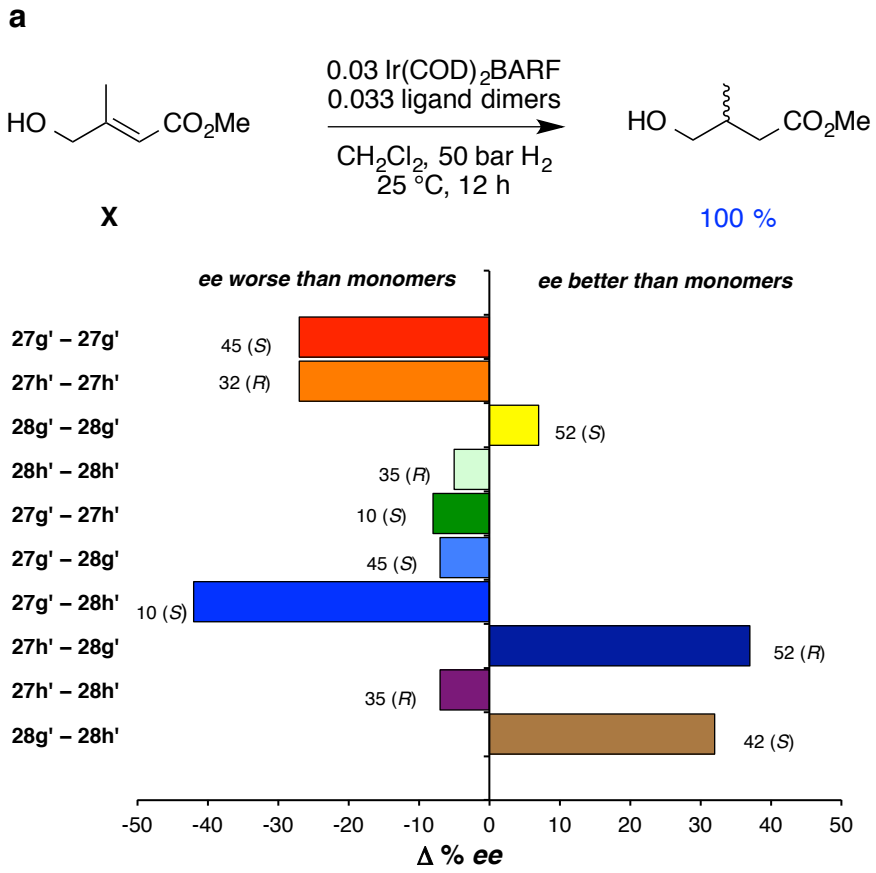


Figure 5.12. Hydrogenation of hydroxyester **X** (**a**) and acetoxyester **Y** (**b**) using catalysts from the monodentate ligands **27g**, **27h**, **28g**, and **28h** after metathesis (as in Figure 5.4) then addition of $Ir(COD)_2^+$. The bars are calibrated to the corresponding combination of monodentate ligands, and the overall enantioselectivities are indicated by the numbers on the bars.

b

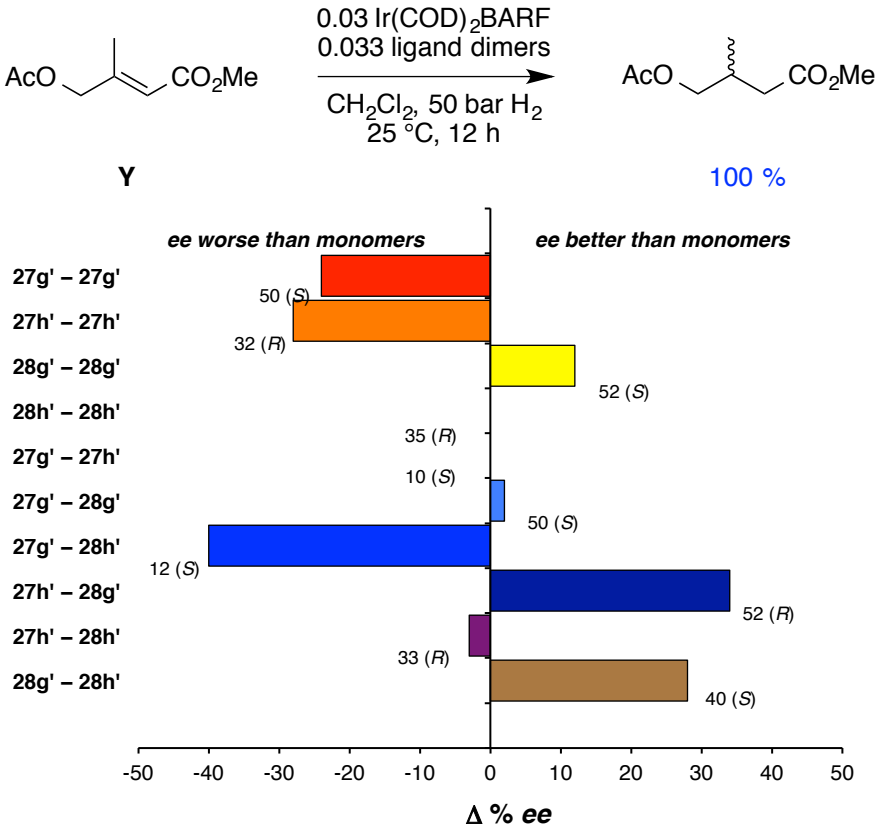


Figure 5.12. continued.

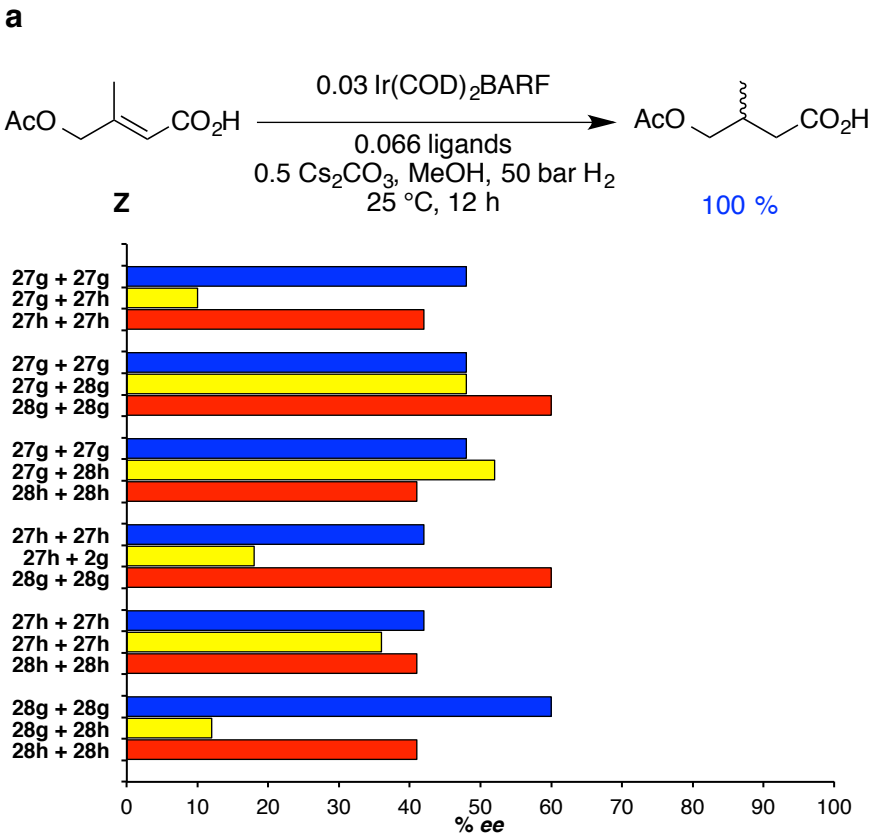


Figure 5.13. Hydrogenation of the acetoxy acid **Z** using: **a** catalysts from the monodentate ligands **27g**, **27h**, **28g**, and **28h**; and **b** from the same ligands after metathesis (as in Figure 5.4). The bars in part **b** are calibrated to the corresponding combination of monodentate ligands, and the enantioselectivities are indicated by the numbers on the bars.

b

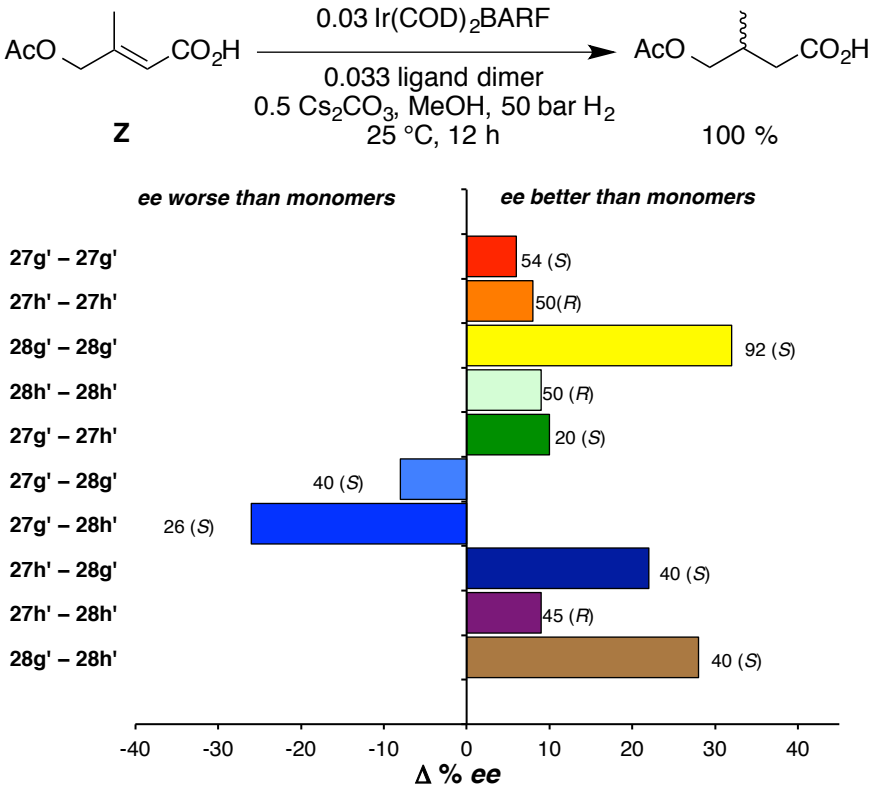


Figure 5.13. continued.

Data was also collected for hydrogenation of the acetoxy acid **Z** with and without metacatalysis using $Rh(COD)_2^+$ {rather than $Ir(COD)_2^+$ as in Figure 5.13}. Some of the reactions with metacatalysis showed improvements relative to the ones without, but the best overall enantioselectivity (75 %) was observed for a monomer combination. This data is shown in the supporting materials.

5.3 Conclusions

These studies have shown that ligands can be formed via metathesis reactions, then used in hydrogenation catalysts formed *in situ*, thus the concept of metathesis then catalysts, *metacatalysis*, is validated. Residual ruthenium complexes from the metathesis steps do not mediate hydrogenations of the substrates studied here. Relative

to controls with monomeric starting materials (series **27** and **28**), metacatalysis can have positive and negative effects on the enantioselectivities (see Figure 5.9 and 5.10b). Only four monomeric starting materials were used (**27g** and **h**, **28g** and **h**) to explore metacatalysis here, but in general for *n* ligands there would be $n(n + 1)/2$ possible combinations; if *n* is a larger number many combinations can be generated (*eg* for $n = 10$, the number of possibilities is 55)[204] so, just like mixing monodentate ligands, this is an effective form of combinatorial catalysis.[205-208] Overall enantioselectivities observed (up to 92 %) were good but not excellent, and there are several obvious reasons why this might be so. Throughout, the bisphosphites formed in this study would form huge chelates if they complexed in the M*PP* form, so they are likely to be somewhat flexible. Moreover, the alkene formed between the two monomeric fragments is almost certainly reduced in these reactions, and rapidly compared with the more substituted alkene substrates, hence the ligands change early in the hydrogenation. On the other hand, one of the objectives we had at the onset of this study was to see if we could find ligands via metacatalysis that were effective despite these factors, and indeed enantioselectivities of up to 92 % *ee* were obtained. Rational design is most effective for relatively simple systems for which some parameters can be predicted with certainty, whereas combinatorial methods tend to be relatively more effective as the opportunities for rational design diminish.

This research has shown that the dominant parameter governing stereodifferentiation by ligands **27** and **28** is the alkoxy *P*-substituent, and binaphthyl was the best studied here. The alkaloid fragment in the ligands has much less impact than the binaphthyl. Metathesis coupling of the alkaloid fragments is relatively slow, requiring 12 h in refluxing dichloromethane, though, given time, conversion to the dimeric forms **27'** and **28'**, was near complete.

The most enantioselective catalyst found in this study was from the metathesis coupling product **2g'** – **2g'** (92 % *ee*, Figure 8b, third entry). This ligand, **2g'** – **2g'**, is a *homo*-combination so it was not necessary to deconvolute mixtures from *hetero*-combinations to find the best ligand-metathesis products: we were able to demonstrate

proof of concept without doing that. This is fortunate because, as alluded to above, the polarities of these particular molecules are dominated by the huge and similar alkaloid parts, hence we were unable to separate the various metathesis combinations even by analytical HPLC. There is an important conclusion to be drawn from this: separations in metacatalysis can be problematic, so the "end game" in the method is likely to be easiest to implement if the alkenes combined have different polarities or other features that make homo- and hetero-combinations separable.

Based on observations from this work, further studies of metacatalysis might focus on ligand fragments that give more distinct differences between homo- and hetero-dimeric products. That strategy would be desirable because mixture analyses would be easier, and the diversity of ligands created would be greater. Another obvious modification would be to use alkene-monomers with potential complexing atoms that are closer to the metathesis site. This strategy would produce smaller chelates, but it is somewhat limited by the undesirable potential for deactivation of the metathesis catalyst by association of the complexing atom to the ruthenium carbene center. For this reason, the design of the alkene-monomers requires careful consideration.

Metacatalysis need not be restricted to hydrogenation reactions. Indeed, one intriguing possibility for alkaloid-based ligands would be to explore oxidation processes including, and related to, Sharpless' dihydroxylations, for which cinchona alkaloids are known to be highly effective.[209] Moreover, there are possibilities for using other transformations to join monomeric fragments *in situ*, the only obvious restrictions being that they should be efficient and generate no by-products that adversely effect the subsequent reactions. We suggest metacatalysis is an option for expanding the combinatorial methodology established by Reetz and others, and it has the advantage of generating diverse, potentially chelating ligands. On a broader level, our method complements others that allow generation of diverse libraries of bidentate ligands by combining monodentate ones;[204,210-237] notably, those include dynamic combinatorial libraries formed from fragments having complementary *H*-bonding topologies.[238-244]

CHAPTER VI
LIGHT ACTIVATED LIGANDS FOR CATALYTIC REACTIONS

6.1 Introduction

Most of catalytic reactions are usually driven by thermal energy or microwave irradiation. These sources of energy mostly eliminated dangerous byproducts; for example, CO_2 from burned charcoal is pollutants leading to global warming. Moreover, both thermal energy and microwave irradiation, at present, use electricity that needs to be produced and hard to be stored. Light, however, is a natural abundance source and excellent green energy that can reduce the use or generation of hazardous chemicals.

Many applications using light mostly involved radical reactions, chemosensors or photosensitizers that generated electron transfer in reactions to be potential ligands for REDOX chemistry (example shown in Figure 6.1). In most cases, especially radical reactions, the purpose of use light as energy is to avoid harsh conditions to overcome activation energy in limiting step; for instance, Heck reaction, one of typical carbon–carbon bond formation, need at least 60 ^{o}C to get good conversion.

Carbon–carbon bond formation using metal catalyzed reaction is useful with widely application in organic synthesis. Instead of using thermal conditions, light can be used to start catalytic cycle via radical reactions. Simple starting materials, however, require high energy to generate radicals; for example, C-H bond requires far UV (l <220 nm) to reach excited state. Improving by lower the energy requirement could be accessible by using photosensitizers to transfer electron or energy to reagents in catalytic cycle (Figure 6.2). Electron transfer in catalysis has usually been studied for reduction of CO_2,[245] but intermolecular processes,[246,247] usually featuring $(bipyridyl)_3Ru(2+)$,[248,249] have been known for some time, even featuring organocatalysis.[250]

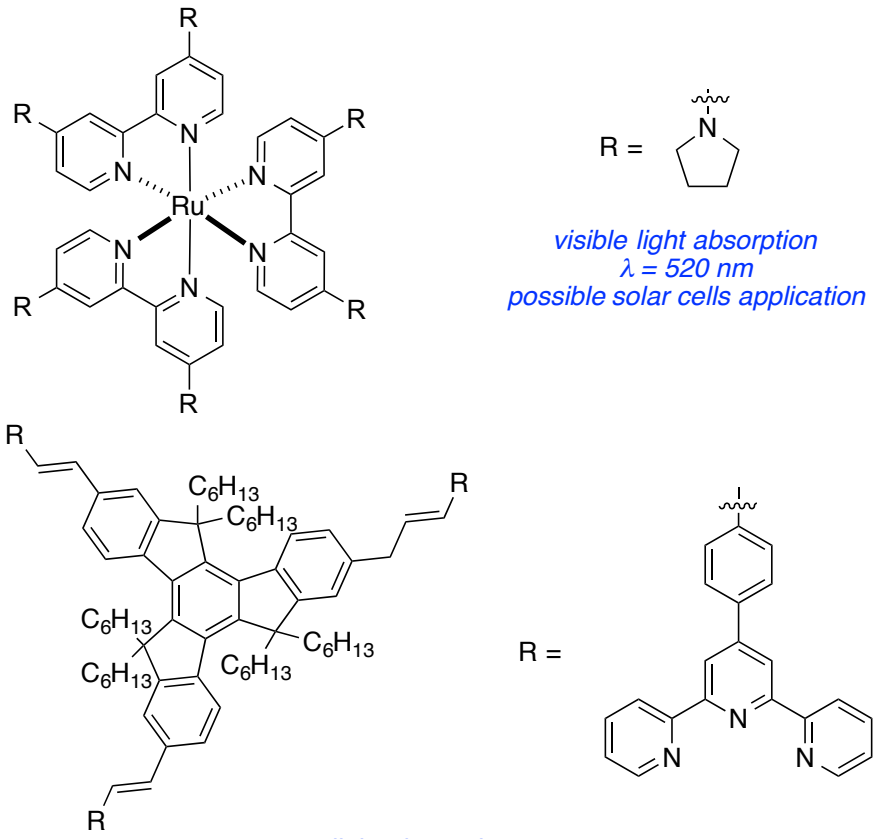


Figure 6.1. Examples of light absorption substrates and their applications.

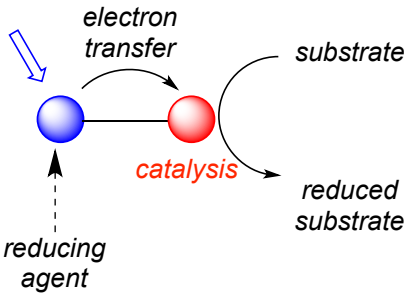


Figure 6.2. Using photosensitizers to transfer electron or energy to reagents in catalytic cycle.

For energy transfer, there are very few examples of photo-driven catalytic reactions.[251] Konig's work is the best one in literature reported about Suzuki/Stille mediated by $Pd(PAr_3)_4$, Ar = pyrene, to couple phenyl boronic acid with $4\text{-}BrC_6H_4Me$ under irradiation at 361 – 375 nm from a UV diode array (Figure 6.3b).[252] The results indicated reactions gave selectivity for heterocoupling products. Furthermore, reactions did not proceed in the dark, but proceed again when light was irradiated. Other examples feature ruthenium complexes in which ruthenium is in electronic communication with palladium.[253,254] This complex has been shown to mediate head-to-tail coupling of 2-phenylpropene (Figure 6.3c).

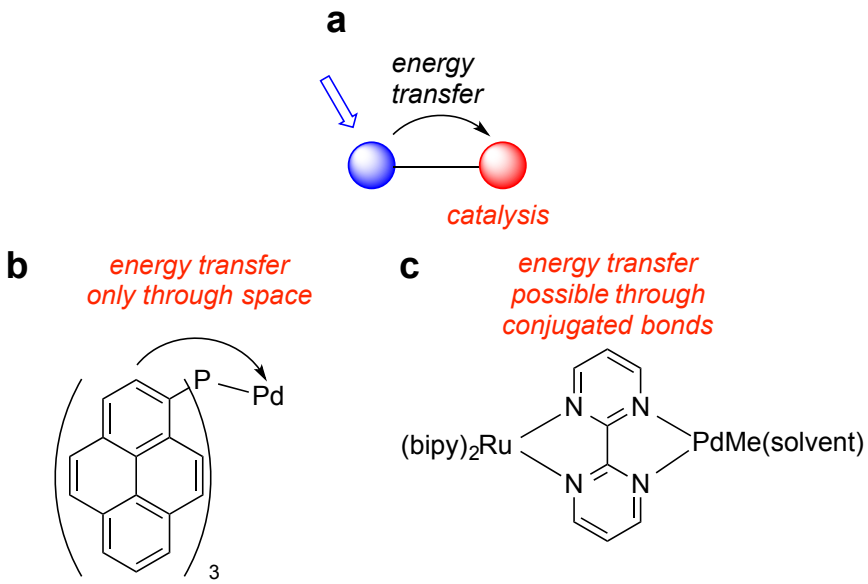


Figure 6.3. **a** Energy transfer diagram for catalytic reactions and examples of catalysts; **b** Pd catalyst for Suzuki/Stille reactions and **c** Ru /Pd for polymerization.

Our group has been interested in the energy transfer, but not electron transfer, and has synthesized many dyes for cell-imaging works. We, however, never use those dyes in light activated catalytic reaction because they lack of ability to become ligand to metal.

As a result, we proposed to synthesize ligands that could be effective and suitable for photo-driven catalysis. The desired ligands were considered to have chromophores

that absorb UV visible light with high absorptivities, and would otherwise fluoresce. Moreover, these chromophores should be connected to metal by electronic conjugation (Figure 6.4), so that energy transfer to the metal can take place through bonds, as well as through space. By using direct conjugation, we hypothesized that energy transfer will be similarly efficient to cell-imaging dyes and could be applied to ligands in photo-driven catalysis.

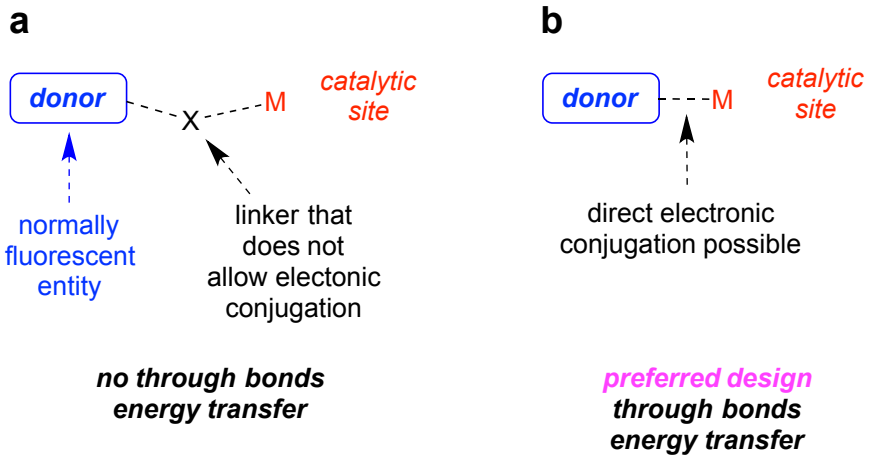


Figure 6.4. Energy transfer from donor to metal by through space energy transfer **a**; and through bond energy transfer **b**.

To get the best advantage, we proposed to use Heck reaction. In general, this reaction using phosphine ligands usually requires high temperature and high catalyst loading. Carbene ligands, however, could help decrease catalyst loading to about 0.1 – 1 %. There, we desired to synthesize the carbenes attached with chromophores and studied the Heck reaction using low temperature.

6.2 Results and discussion

We proposed to synthesize ligands that could be effective and suitable for photo-driven catalysis. The desired ligands were considered to have chromophores that absorb UV visible light with high absorptivities, and would otherwise fluoresce. Carbenes ligands were suitable in this case because they conjugate directly to the metal and

catalysts could be used in many catalytic reactions. Moreover, pyrene was selected as chromophore due to it strong absorbance under UV-visible (Figure 6.5).

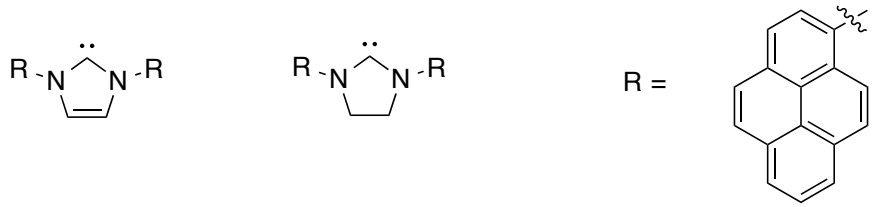
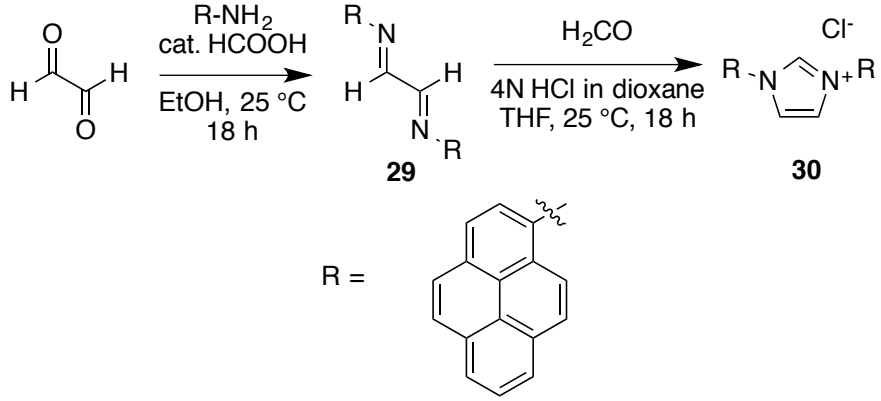
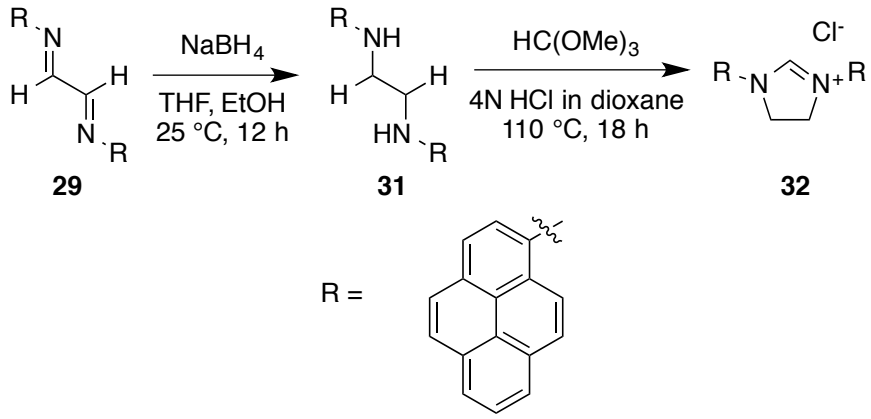


Figure 6.5. *N*-Heterocyclic carbenes containing pyrene as chromophore.

Precursors of carbenes, imidazolium and imidazolinium salts were synthesized from same diimine starting materials that was obtained from condensation of 1-aminopyrene with glyoxal under acidic condition. Reaction of diimine with formaldehyde gave imidazolium salt about 85 % (Scheme 6.1). To obtain another carbine precursor, diimine was reduced to corresponding diamine followed by condensation with trimethyl orthoformate yield imidazolinium salt about 78 % (Scheme 6.2).



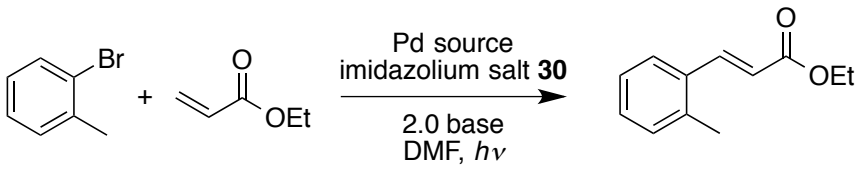
Scheme 6.1. Synthesis of imidazolium salt **30**.



Scheme 6.2. Synthesis of imidazolinium salt **32**.

Table 6.1 shows the results of Heck reactions using ethyl acrylate and 2-bromotoluene. Pd sources, catalyst loading, bases, and solvent varied to obtain optimization condition. Unfortunately, the highest conversion of the reaction was only 3 % conversion when imidazolium salt was used as precursor of carbene combined with 0.05 $Pd_2(dba)_3$ and ^tBuOK. The rest of conditions gave only trace amount of product. Same results were obtained when imidazolinium salt was used as a carbene precursor as shown in Table 6.2.

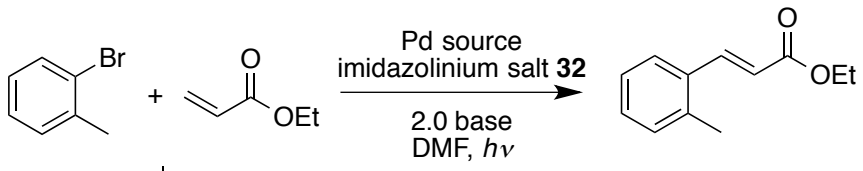
Table 6.1. Heck reactions using imidazolium salt **30** as light activated ligands.



Pd	Pd (eq)	Base	Alkene (eq)	Solvent	Conversion (%)[a]
$Pd(OAc)_2$	0.01	^{t}BuOK	1	DMF	trace
$Pd(OAc)_2$	0.01	^{t}BuOK	1	THF	trace
$Pd(OAc)_2$	0.01	^{t}BuOK	1	EtOH	trace
$PdCl_2$	0.01	^{t}BuOK	1	THF	trace
$Pd_2(dba)_3$	0.01	^{t}BuOK	1	THF	<1%
$Pd_2(dba)_3$	0.01	^{t}BuOK	10	THF	2%
$Pd_2(dba)_3$	0.05	^{t}BuOK	10	THF	3%
$Pd_2(dba)_3$	0.01	K_2CO_3	10	THF	<1%
$Pd_2(dba)_3$	0.01	Cs_2CO_3	10	THF	<1%

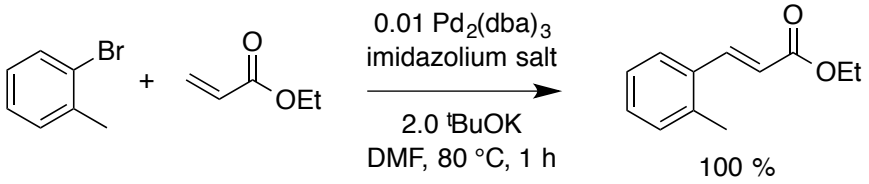
[a]Conversion determined by GC

Table 6.2. Heck reactions using imidazolinium salt **32** as light activated ligands.



Pd	Pd (eq)	Base	Alkene (eq)	Solvent	Conversion (%)[a]
$Pd(OAc)_2$	0.01	^{t}BuOK	1	DMF	trace
$Pd(OAc)_2$	0.01	^{t}BuOK	1	THF	trace
$Pd_2(dba)_3$	0.01	^{t}BuOK	1	EtOH	trace
$Pd_2(dba)_3$	0.05	^{t}BuOK	5	THF	2%
$Pd_2(dba)_3$	0.05	^{t}BuOK	10	THF	3%

After all results in Table 6.1 and 6.2, we were curious that the ligands were suitable for Heck reaction. Therefore, we performed the standard thermal Heck coupling conditions using the imidazolium salt as light activated ligand (reaction 6.1). The results indicated that 60 % conversion was obtained in 30 min using 60 °C in DMF and reaction reached 100 % conversion at 80 °C in 1 h.

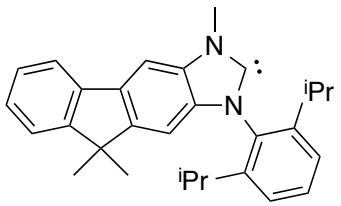


reaction 6.1

All results indicated that the new light absorbing carbenes were excellent ligands for Heck coupling under thermal condition but unable to perform as the catalyst using light activation. Considered of both precursors of carbene, there is possibility that

pyrene is big and forms perpendicular with core of imidazole. Therefore, the pyrene would possibly not conjugate with imidazole leading to only through space energy transfer in the reaction that was not the proposed of our study.

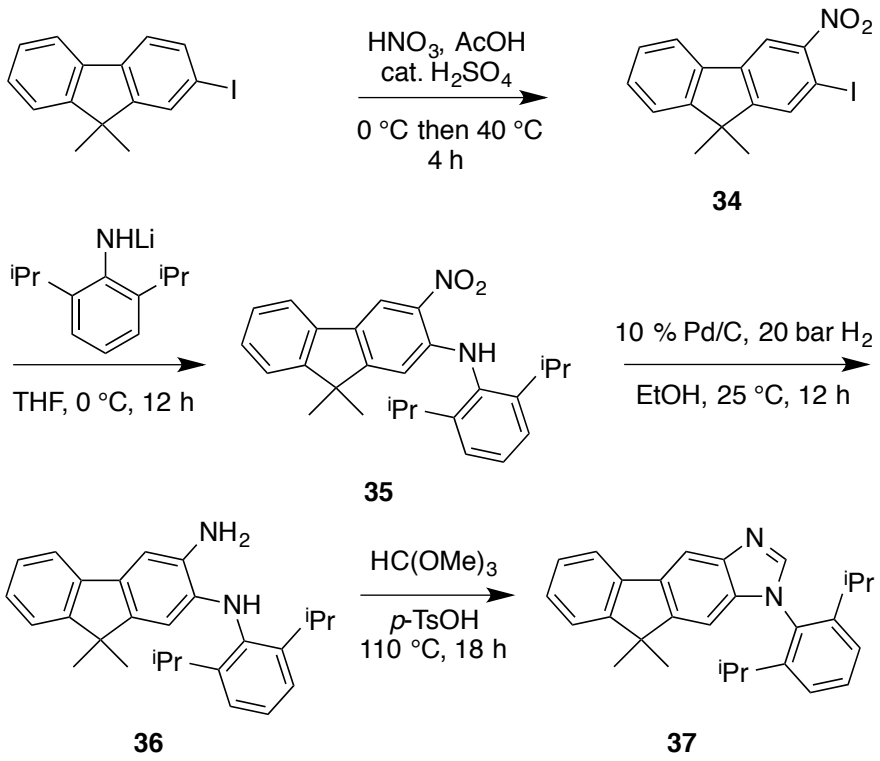
Therefore, we designed a new carbene ligand **33** (Figure 6.6) to obtain good conjugation; it has strong absorption and fluorescence. As a result, fluorene, the precursor of many dyes, was chosen as the best choice because of its absorption and commercially available.



33

Figure 6.6. Structure of compound **33**.

2-Iodofluorene was synthesized by the known method[255] followed by alkylation under basic condition yielded 9,9-dimethyl-2-iodofluorene. Nitration followed by S_NAr with 2,6-diisopropylaniline gave 2-amino-9,9-dimethyl-3-nitrofluorene derivative. The product, then, was reduced to give 2,3-diamine derivatives. Finally, reduction product was reacted with trimethyl orthoformate under acid condition give fluorene-2,3-imidazole **37** (Scheme 6.3).

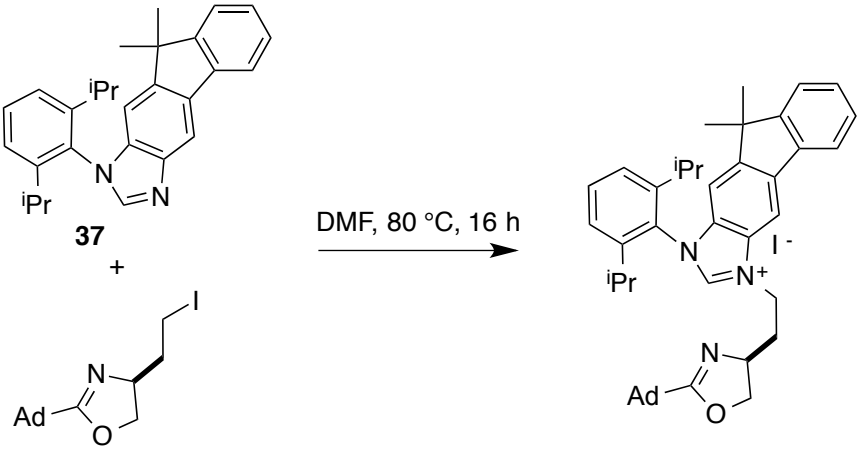


Scheme 6.3. Synthesis of imidazole **37** from fluorene derivatives.

The final imidazole was investigated in two ways. First, reaction of resulting imidazole with methyliodide yielded imidazolium salt as carbene precursor to study Heck reactions as previously mentioned above (reaction 6.4). Second, the same imidazole was reacted with iodo-oxazoline[30] to give the corresponding carbene precursors that were converted to the iridium complexes (Scheme 6.4). The final complex was used for studying hydrogenation of unfunctionalized alkenes or alkenes without coordinating functional groups.

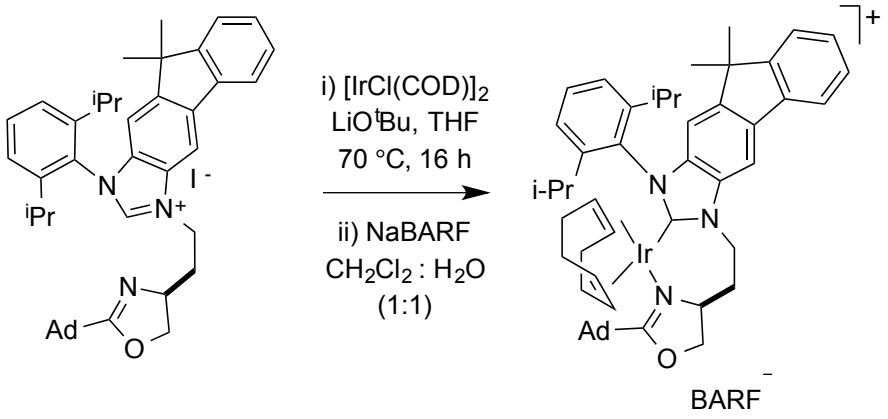
37 **33**

reaction 6.2



38

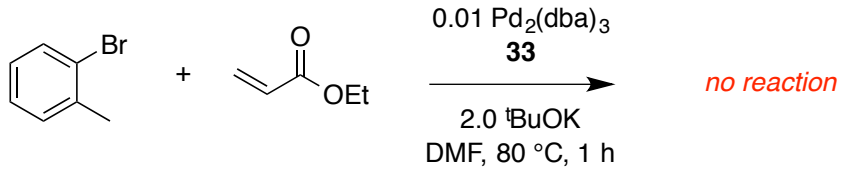
reaction 6.3



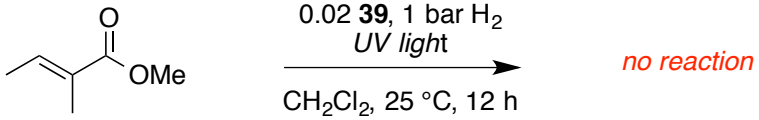
38 **39**

Scheme 6.4. Synthesis of hydrogenation catalyst **39** containing chromophore derived from fluorene.

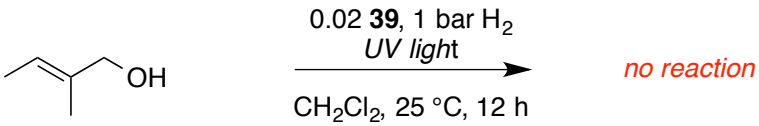
Using the same conditions for Heck reaction previously mentioned above, imidazolium ligand (**33**) derived from fluorene, unfortunately, could not be able to give the product under both thermal and light activated conditions (reaction 6.4). Therefore, we moved our attention to the asymmetric hydrogenation reaction. First, α-methylstilbene was tested to confirm that catalyst was effective and excellent conversion was obtained with good stereoselectivity. Other substrates, then, were tested using Burgess' oxazoline-imidazole iridium catalyst to confirm that they cannot be hydrogenated under 1 bar of H_2. Methyl tiglate (reaction 6.5), tiglic alcohol (reaction 6.6), and cyclic compounds were chosen to investigate hydrogenation. The new light activated catalyst, however, cannot perform any hydrogenation.



reaction 6.4



reaction 6.5



reaction 6.6

To explain this situation, we tested UV and fluorescence to the new catalyst. The results indicated that the new catalyst absorbed at the new wavelength compared to precursor ligand and fluorescence at another wavelength. As a result, a wavelength used for activation would excite the new catalyst without energy transfer to metal and the activated catalysts might not be suitable for any reaction due to their excited state.

The results from Heck reaction could be explained using thermal condition. We believed that the activated catalyst released the fluorescence acted as new source of energy for reaction. As a result, the solution mixture was little heated up cause the Heck reaction to yield the products up to only 3 %.

6.3 Conclusions

The new carbene precursors with chromophore for light absorption catalytic reaction, *N*,*N*'-dipyrenyl-imidazolium salt, *N*,*N*'-dipyrenyl-imidazolinium salt and fluorene-2,3-imidazole, were synthesized and used to investigate Heck reactions and asymmetric hydrogenations. The carbene ligands with chromophores were excellent catalyst under thermal conditions as shown in Heck reactions. The catalysts, however, could not perform as light activated catalysts under room temperature. Moreover, the new fluorene-2,3-imidazole ligand also could not be used in asymmetric hydrogenation because whole molecule of catalysts were probably excited without energy transfer. To investigate performance of catalysts further, REDOX reactions probably gave some results that could be suitable for the energy and electron transfer in catalytic reactions.

CHAPTER VII

SYNTHESIS AND INVESTIGATION OF NEW *P*,*N*-LIGANDS DERIVED FROM 2-OXO-IMIDAZOLINE FOR ASYMMETRIC HYDROGENATION

7.1 Introduction

During the past decades, stereoselective hydrogenations have gained attention by several chemists because it is an attractive methodology used for synthesizing natural products. Many chiral analogs of Crabtree's catalysts were synthesized and studied hydrogenation of unfunctionalized alkenes. Moreover, they were applied to hydrogenate alkenes without coordinating functional groups, such as ester, silyl ether, enol ethers, *etc*.[11,16,21,84] Even though several catalysts have been introduced, none of these catalysts is perfect for hydrogenation every substrate. Design of the new ligands is one possible method to screen and discover new excellent catalysts.

Imidazoles and imidazolines were often used as sources of *N*-heterocyclic carbene ligands. The 2-substituted-imidazoles and -imidazolines, however, cannot be used for this purpose. The compounds can be used as ligands for asymmetric catalysis because they have two nitrogens to serve as coordination sites. Figure 7.1 shows examples of ligands derived from imidazole that use nitrogen as chelation part. Using this new designed complexes were able to perform as promising candidates for application in a wide range of asymmetric reactions such as the Henry reaction,[256] conjugate addition,[257] addition of dialkylzinc to aldehydes,[258] allylation,[259] epoxidation and cyclopropanation, [260] oxidation[261] or transfer hydrogenation.[262]

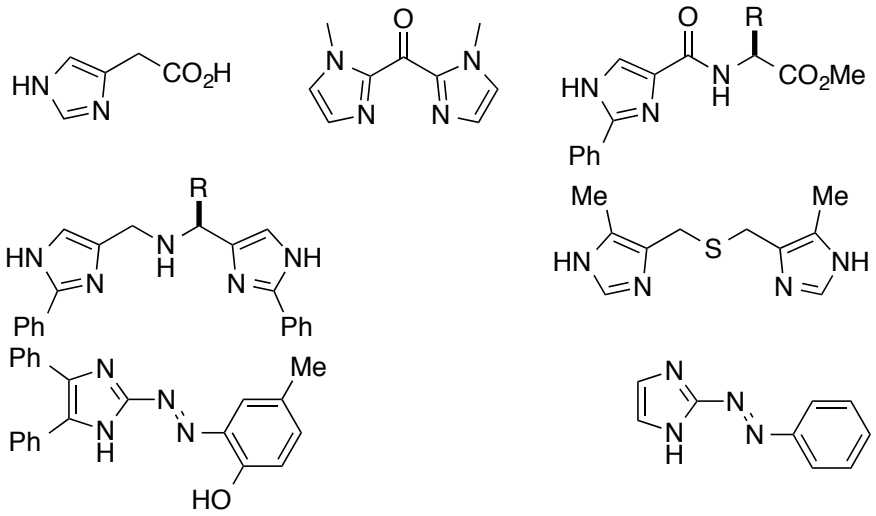
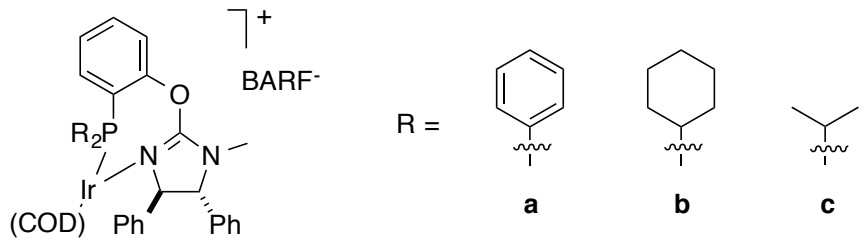


Figure 7.1. Examples of imidazoles derivatives served as *N*-chelation ligands.

To the best of my knowledge, most of catalysts synthesized so far using *N*-chelation from oxazolines, pyridines, primary amines, and thiazoles. In this project, I would like to introduce the first chiral analogs of Crabtree's catalyst **40** derived from phosphine and 2-oxo-imidazoline derived from (*R*),(*R*)-1,2-diphenylethylenediamine (Figure 7.2). Different commercially available phosphines have been used to synthesize a small library of ligand in this set for comparison resulting to finding high stereoselective ligands for unfunctionalized and non-coordination functional group alkenes.

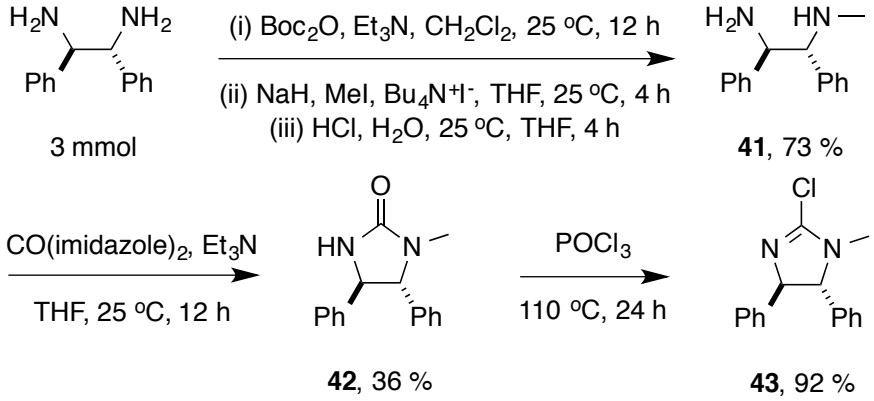


40

Figure 7.2. Structure of new hydrogenation *P,N*-iridium catalysts derived from 2-oxo-imidazoles.

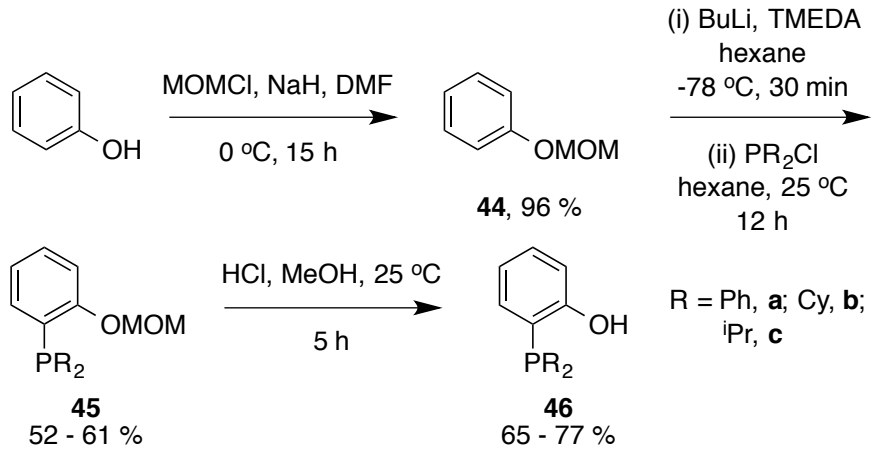
7.2 Results and discussion

Syntheses of catalysts were divided into two parts, 2-chloro-imidazoline derivatives and 2-dialkylphosphino-phenol. The former was synthesized by using BOC protected (*R*),(*R*)-1,2-diphenyl-ethylenediamine, prepared using a known literature procedure,[263] reacted with iodomethane to form *N*,*N'*-di(BOC)-N-methyl-(*R*),(*R*)-1,2-diphenyl-ethylenediamine. Deprotection of the BOC group gave mono-*N*-alkylated product **41**, *N*-methyl-(*R*),(*R*)-1,2-diphenyl-ethylenediamine, in moderate yield. Compound **41** was reacted with 1,1-carbodiimidazole to obtain *N*-methyl-4,5-diphenylimidazolidin-2-one which was converted to 2-chlro-*N*-methyl-4,5-diphenylimidazolidine using phosphorus oxychloride (Scheme 6.1).



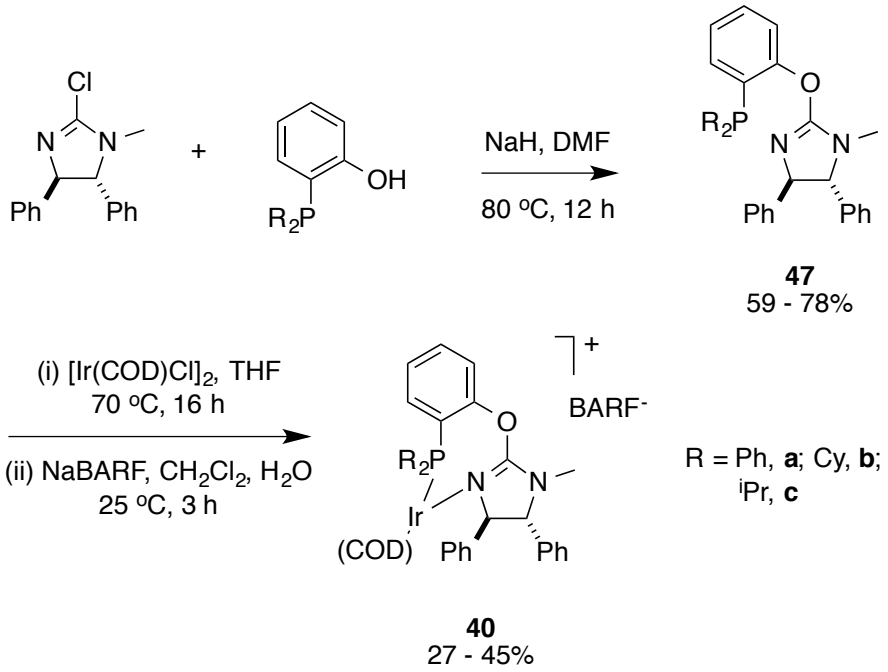
Scheme 7.1. Synthesis of 2-chloro-*N*-methyl-4,5-diphenylimidazolidine.

The phosphine parts were synthesized strarting from MOM-protected phenol. Directing group *ortho*-deprotonation compounds using *n*-butyllithium were reacted with corresponding electrophiles, chlorodisubstitutedphosphine, to obtain 2-dialklphosphino-MOM-protected phenol.[264] MOM-Deprotection under acid condition gave 2-dialkylphosphino phenols (Scheme 6.2) in good yield. Three different phosphines, *e.g.* phenyl, cyclohexyl and isopropyl, were chosen to study steric and electronic properties of the catalysts **40**.



Scheme 7.2. Syntheses of 2-dialkylphosphino-phenol.

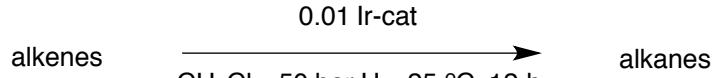
After getting two parts in-hand, phenol derivatives were reacted with 2-chloro-*N*-methyl-4,5-diphenylimidazolidine under basic condition to obtain the corresponding ligands. Reaction of the appropriated ligands with $[Ir(COD)Cl]_2$ followed by anion exchange with NaBARF gave the corresponding catalysts **40** in moderate yield (Scheme 6.3). According to this procedure, all catalysts were obtained by using cheap starting material except the chiral (*R*),(*R*)-1,2-diphenyl-ethylenediamine. Even though the procedure is easy, the product of many reactions need to be purified by flash chromatography under a harsh condition such as CH_2Cl_2, $CHCl_3$ and MeOH.

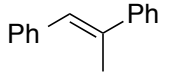
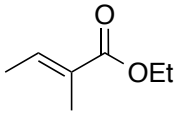
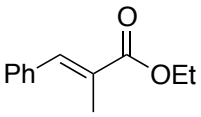
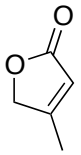
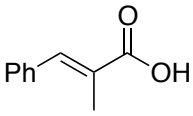


Scheme 7.3. Syntheses the *P*,*N*-iridium catalyst **40** for asymmetric hydrogenation.

Table 7.1 shows the hydrogenation results using catalysts **40a – c**. Hydrogenation of unfunctionalized alkene, 1,2-diphenylpropane, was first investigated using these catalysts because it is the most widely studied substrate for asymmetric hydrogenations using chiral Crabtree's catalyst analogs.[16] The results indicated that these catalysts were effective as hydrogenation catalyst with good enantioselectivities. Substrates without coordinating functional group, especially acyclic and cyclic esters, were then hydrogenated to obtain the moderate selectivities. The results showed that catalyst **40c,** the diisopropylphosphino phenol derivative, was the best catalyst in most cases. The only case that catalyst **40b** give better result than **40c** is the hydrogenation of lactone that **40b** can give 28 % *ee*. Only one olefin with coordinating functional group, carboxylic acid, was tested in this study. The results, however, indicated that all catalysts were not suitable for both lactone and carboxylic acid substrates.

Table 7.1. Hydrogenation result using Ir-catalyst **40**.



Alkenes	40		
	a	**b**	**c**
	91	93	94
	55	58	60
	50	55	75
	10	28	15
	18	28	30

According to data obtained from Table 7.1, further study can be possible achieved by synthesizing more catalysts using many commercially available phosphines to make a larger library and then investigate the asymmetric hydrogenation to obtain better selectivities. Moreover, only one chiral, (*R*),(*R*)-1,2-diphenyl-ethylenediamine, was used in this study. Other chiral ethylenediamines can be used to prepare 2-chloro-imidazolines to compare different chiral environment for asymmetric reactions. Another investigation of this research can be obtained from different alkene substrates because it is possible that the catalysts were suitable for substrates that were not included in this study.

7.3 Conclusions

The new chiral analogs of Crabtree's catalyst derived from 2-oxo-imidazoline were introduced and proved to be effective for hydrogenation reactions with unfunctionalized alkenes. In addition, the catalysts were also used to hydrogenate olefin without coordinating functional group provided moderate enantioselectivities for acyclic ester derivatives and poor stereoselectivity for cyclic ester. In order to gain higher selectivity, synthesis of larger library should be obtained to find the best catalyst in this structure. Moreover, the catalyst might not be suitable for the compounds tested in this study. Varying the substrates might provide suitable structures that can be hydrogenated with high stereoselectivities.

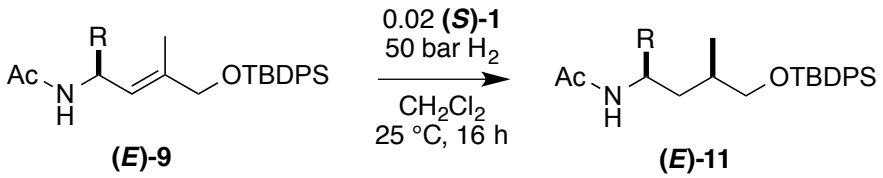
CHAPTER VIII
CONCLUSIONS AND OUTLOOK

8.1 Conclusions

8.1.1 Syntheses useful chirons using chiral Crabtree's catalyst

Asymmetric hydrogenations of non- or weakly-coordinating functional group alkenes have been used to prepared useful chirons for syntheses many natural products. Chiral analogs of Crabtree's catalyst have privilege to this type of alkenes yielded high stereoselectivities. Several substrate vectors were used to obtain the highest stereoselectivities by manipulating: (i) protecting groups; (ii) functional groups; and (iii) alkene geometry.

We have demonstrated the application of Chiral Crabtree's catalysts, especially catalyst **1**, for hydrogenation allylic amines as new approaches to α,γ-amino acid derivatives. The excellent diastereoselectivities of hydrogenation provided an opportunity to apply this method to chiral natural products with different substituents varying from α-amino acids.



R = Bn, **a**; Me, **b**; ^{i}Pr, **c**; CH_2OBn, **d**;
$CH_2(4\text{-}BnOC_6H_4\text{-})$, **e**.

Figure 8.1. Useful compounds from chirons prepared via stereoselective hydrogenation.

Catalyst **1** has also been applied to scalable synthesis of *homo*-Roche ester which could give more than ten grams of product. The catalyst, however, gave only good but not excellent selectivity up to 94 % *ee*. Fortunately, the *homo*-Roche ester could be converted to five-membered lactone and then recrystallized under cold condition to provide enantioenriched *homo*-Roche ester. Modification of this compound to generate

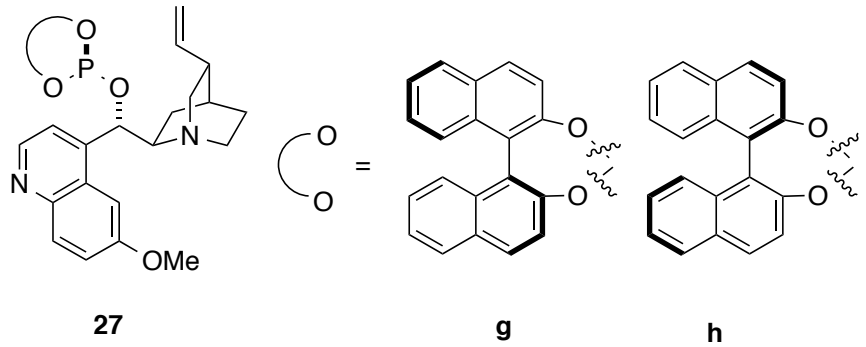
α-substituted homo-Roche ester derivatives via organocatalysis has provided useful compound such as γ-hydroxyvaline.

8.1.2 Varying electronic effect using different carbenes as new catalysts for hydrogenation

Structure of catalyst **1** can be easily modified using different *N*-heterocyclic carbenes, imidazolinylidene and benzimidazolylidene. Three different *N*-heterocyclic carbenes provided different electronic effect to the iridium catalysts. New iridium catalysts have performed as good asymmetric hydrogenation catalysts. The results indicated that small electronic effect could be negligible and catalysts provided no different catalytic activity in term of stereselectivity.

8.1.3 Syntheses new ligands with *N*,*P* and *P*,*P*-iridium catalysts for asymmetric hydrogenation

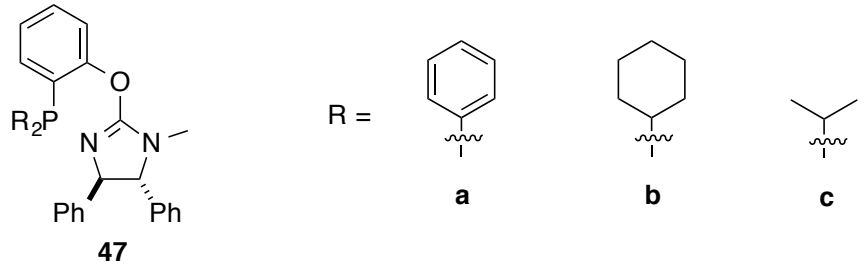
Many new ligands were synthesized using to investigate asymmetric hydrogenation of largely unfunctionalized alkenes such as esters, alcohols and carboxylic acids. First, the new ligands contained cinchona alkaloid phosphite derivatives to give monodentate ligands. The results indicated that the phosphite containing quinidine, or quinine, and binaphthol (Figure 8.2) gave the best stereoselectivity in this series. This study also showed that combination of metathesis to convert *mono*-dentate into *bi*-dentate ligands with catalysis (in here refer to "*metacatalysis*") could give the better selectivity in some cases.



27 **g** **h**

Figure 8.2. Example of new ligands derived from quinidine and binaphthol.

Second, another ligands were redesigned to use different *N*-chelating site synthesized from 2-oxo-imidazoline to give new phosphine-2-oxo-imidazoline ligands (Figure 8.3). The new *P*,*N*-iridium catalysts were proved to be effective as asymmetric hydrogenation catalyst on certain substrates.



47 **a** **b** **c**

Figure 8.3. New ligands derived from 2-oxo-imidazoline.

Finally, *N*-heterocyclic carbenes were modified to have chromophores (Figure 8.4). These gave new ligands that have an ability to absorb UV-Visible light and possibly used light to activate the catalysts. Even though, the ligands were effective in Heck reactions under thermal condition. They, unfortunately, were ineffective under light absorption condition. Moreover, the same results were obtained from hydrogenation reaction.

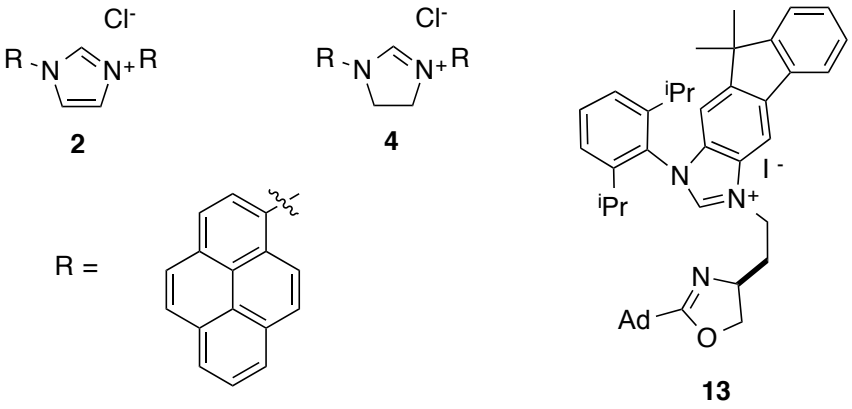


Figure 8.4. New ligands with chromophores for light absorption reactions.

8.2 Outlook

8.2.1 Syntheses of natural products via hydrogenations

During my research studies, our group has developed many methodologies for the syntheses of many chiral building blocks. One of my research studies was involved with syntheses of γ-amino acid derivatives that could be used to synthesize part of tubulysins, potential anticancer natural products isolated from a strain of myxobacteria (Figure 8.5).

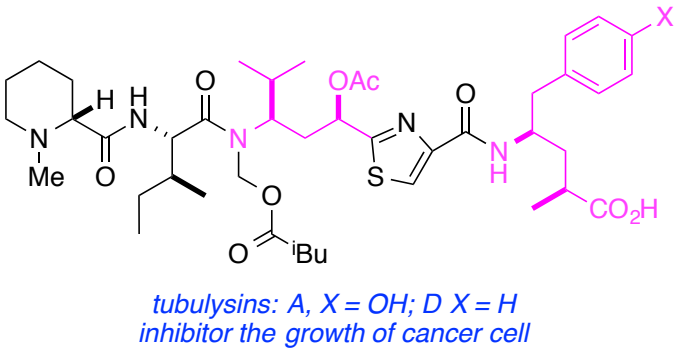


Figure 8.5. Tubulysins, natural products containing γ-amino acid derivatives.

According to the structure, tubulysins contained another γ-amino acid derivatives but not the one in my research. Previous data from Dr. Ye Zhu in our group indicated that catalyst **1** could hydrogenate enol ethers without isomerization. Combination of

both data gave possible opportunity to hydrogenate alkene in Figure 8.6 in order to obtain another fragment then connected with the other amino acids to obtain tubulysins.

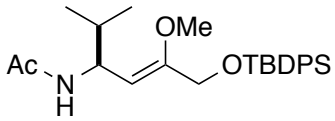


Figure 8.6. Other alkene fragment that possibly be hydrogenated with catalyst **1**.

8.2.2 Syntheses of new energy transfer ligand for light activation reaction

Due to the energy transfer problems, the next investigation of the project might be using the longer conjugation with some connections that allow direct through-bond energy transfer; for examples, triazole synthesized from click chemistry and alkyne could be used to extend the conjugation (Figure 8.7). Using this method, the absorption energy would be only at the chromophores then energy could transfer to the metal catalytic site to activate the catalytic reaction.

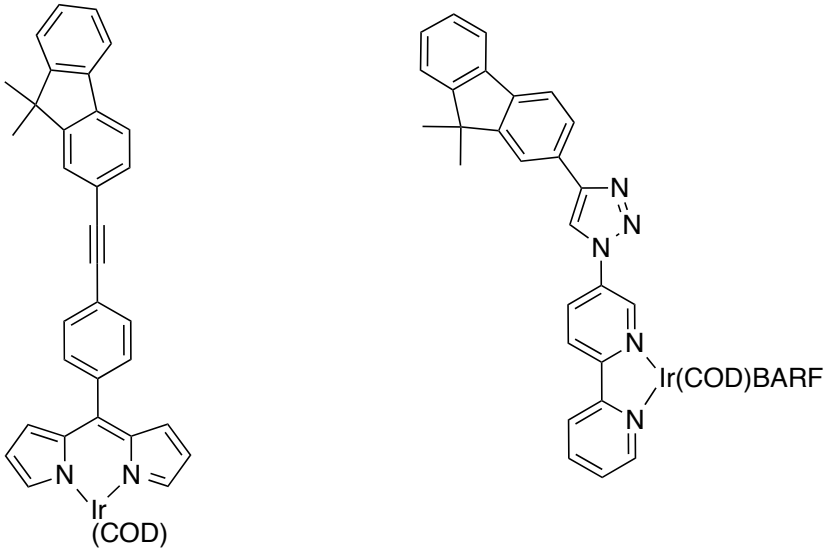


Figure 8.7. *N*-Heterocyclic carbenes containing pyrene as chromophore.

REFERENCES

(1) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951.

(2) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103.

(3) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(4) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

(5) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.

(6) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878.

(7) Leites, L. A.; Magdanurov, G. I.; Bukalov, S. S.; Nolan, S. P.; Scott, N. M.; West, R. *Mendeleev Commun.* **2007**, *17*, 92.

(8) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(9) Leuthaeusser, S.; Schwarz, D.; Plenio, H. *Chem. - Eur. J.* **2007**, *13*, 7195.

(10) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485.

(11) Khumsubdee, S.; Burgess, K. *ACS Catal.* **2013**, *3*, 237.

(12) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278.

(13) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.

(14) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267.

(15) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(16) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

(17) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402.

(18) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33.

(19) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.

(20) Smidt, S. P.; Zimmermann, N.; Studer, M.; Pfaltz, A. *Chem.--Eur. J.* **2004**, *10*, 4685.

(21) Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. *J Am Chem Soc* **2010**, *132*, 1172.

(22) Chakka, S. K.; Peters, B. K.; Andersson, P. G.; Maguire, G. E. M.; Kruger, H. G.; Govender, T. *Tetrahedron Asymmetry* **2010**, *21*, 2295.

(23) Mazuela, J.; Verendel, J. J.; Coll, M.; Schaffner, B.; Borner, A.; Andersson Pher, G.; Pamies, O.; Dieguez, M. *J Am Chem Soc* **2009**, *131*, 12344.

(24) Han, Z.; Wang, Z.; Zhang, X.; Ding, K. *Angew Chem Int Ed Engl* **2009**, *48*, 5345.

(25) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Heterocycles* **2008**, *76*, 771.

(26) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8274.
(27) Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. *J Am Chem Soc* **2006**, *128*, 12886.
(28) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943.
(29) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445.
(30) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878.
(31) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.
(32) Zhu, Y.; Fan, Y.; Burgess, K. *J. Am. Chem. Soc.* **2010**, *132*, 6249.
(33) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem. Eur. J.* **2007**, *13*, 7162.
(34) Cui, X.; Fan, Y.; Hall, M. B.; Burgess, K. *Chem. Eur. J.* **2005**, *11*, 6859.
(35) Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688.
(36) Brandt, P.; Hedberg, C.; Andersson, P. *Chem. Eur. J.* **2003**, *9*, 339.
(37) Schrems, M. G.; Pfaltz, A. *Chem. Commun.* **2009**, 6210.
(38) Franzke, A.; Pfaltz, A. *Chem.-Eur. J.* **2011**, *17*, 4131.
(39) Franzke, A.; Voss, F.; Pfaltz, A. *Tetrahedron* **2011**, *67*, 4358.
(40) Woodmansee, D. H.; Mueller, M.-A.; Neuburger, M.; Pfaltz, A. *Chem. Sci.* **2010**, *1*, 72.
(41) Ganic, A.; Rageot, D.; Trondlin, L.; Pfaltz, A. *Chimia* **2012**, *66*, 187.
(42) Rageot, D.; Woodmansee, D. H.; Pugin, B.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 9598.
(43) Zalubovskis, R.; Hoermann, E.; Pfaltz, A.; Moberg, C. *ARKIVOC* **2008**, 58.
(44) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194.
(45) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023.
(46) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61.
(47) Bernardinelli, G. H.; Kundig, E. P.; Pfaltz, A.; Radkowski, K.; Zimmermann, N.; Neuburger-Zehnder, M. *Helv. Chimica Acta* **2001**, *84*, 3233.
(48) Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70.
(49) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40.
(50) Blankenstein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445.
(51) Cozzi, P. G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450.
(52) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442.
(53) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.
(54) Dieguez, M.; Mazuela, J.; Pamies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888.
(55) Li, J.-Q.; Quan, X.; Andersson, P. G. *Chem.--Eur. J.* **2012**, *18*, 10609.

(56) Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pamies, O.; Dieguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634.

(57) Mazuela, J.; Paptchikhine, A.; Pamies, O.; Andersson, P. G.; Dieguez, M. *Chem. Eur. J.* **2010**, *16*, 4567.

(58) Li, J.-Q.; Paptchikhine, A.; Govender, T.; Andersson, P. G. *Tetrahedron: Asymmetry* **2010**, *21*, 1328.

(59) Verendel, J. J.; Andersson, P. G. *J. Chem. Soc., Dalton Trans.* **2007**, 5603.

(60) Dieguez, M.; Mazuela, J.; Pamies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208.

(61) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudoerfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, *6*, 366.

(62) Kaellstroem, K.; Andersson, P. G. *Tetrahedron Lett.* **2006**, *47*, 7477.

(63) Hedberg, C.; Kaellstroem, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995.

(64) Kallstrom, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.

(65) Co, T. T.; Kim, T.-J. *Chem. Commun.* **2006**, 3537.

(66) Chelucci, G.; Marchetti, M.; Malkov, A. V.; Friscourt, F.; Swarbrick, M. E.; Kocovsky, P. *Tetrahedron* **2011**, *67*, 5421.

(67) Metallinos, C.; Van Belle, L. *J. Organomet. Chem.* **2010**, *696*, 141.

(68) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103.

(69) Li, X.; Li, Q.; Wu, X.; Gao, Y.; Xu, D.; Kong, L. *Tetrahedron: Asymmetry* **2007**, *18*, 629.

(70) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513.

(71) Bolm, C.; Focken, T.; Raabe, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1733.

(72) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941.

(73) Xu, G.; Gilbertson, S. *Tetrahedron Lett.* **2003**, *44*, 953.

(74) Cheruku, P.; Paptchikhine, A.; Church Tamara, L.; Andersson Pher, G. *J Am Chem Soc* **2009**, *131*, 8285.

(75) Wang, D. Y.; Hu, X. P.; Deng, J.; Yu, S. B.; Duan, Z. C.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 4408.

(76) Huang, Y.; Berthiol, F.; Stegink, B.; Pollard, M. M.; Minnaard, A. J. *Adv. Synth. Catal.* **2009**, *351*, 1423.

(77) Goulioukina, N. S.; Dolgina, T. y. M.; Bondarenko, G. N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397.

(78) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536.

(79) Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. G. *Adv. Synth. Catal.* **2008**, *350*, 1168.

(80) Engman, M.; Cheruku, P.; Tolstoy, P.; Bergquist, J.; Voelker, S. F.; Andersson, P. G. *Adv. Synth. Catal.* **2009**, *351*, 375.

(81) Kaellstroem, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575.
(82) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 5595.
(83) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659.
(84) Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, *350*, 979.
(85) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson Pher, G. *Chem Commun (Camb)* **2009**, 5996.
(86) Cheruku, P.; Church, T. L.; Trifonova, A.; Wartmann, T.; Andersson, P. G. *Tetrahedron Lett.* **2008**, *49*, 7290.
(87) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366.
(88) Baeza, A.; Pfaltz, A. *Chem.--Eur. J.* **2009**, *15*, 2266.
(89) Zhou, T.; Peters, B.; Maldonado Matias, F.; Govender, T.; Andersson Pher, G. *J. Am. Chem. Soc.* **2012**, *134*, 13592.
(90) Zhu, Y.; Burgess, K. *Acc. Chem. Res.* **2012**, *45*, 1623.
(91) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581.
(92) Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8584.
(93) Zhu, S.-f.; Yu, Y.-B.; Li, S.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8872.
(94) Zhang, Y.; Han, Z.; Li, F.; Ding, K.; Zhang, A. *Chem. Commun.* **2010**, *46*, 156.
(95) Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 1172.
(96) Johnston, G. A. R. *Curr. Top. Med. Chem.* **2002**, *2*, 903.
(97) Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427.
(98) Johnston, G. A. R. *Phrmacol. Ther.* **1996**, *69*, 173.
(99) Bowery *Eur. J. Pharmacol.* **1981**, *71*, 53.
(100) Hardman, J. G.; Limbird, L. E.; Goodman, G. A. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; 10th ed.; McGraw-Hill: New York, 2001.
(101) McGeer, P. L.; McGeer, E. G. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*; 4th ed.; Raven: New York, 1989.
(102) Sachais, B. A.; Logue, J. N.; Carey, M. S. *Arch Neurol* **1977**, *34*, 422.
(103) Fromm, G. H.; Terrence, C. F.; Chattha, A. S.; Glass, J. D. *Arch Neurol* **1980**, *37*, 768.
(104) Costantino, G.; Macchiarulo, A.; Guadix, A. E.; Pellicciari, R. *J. Med. Chem.* **2001**, *44*, 1827.
(105) Yuen, P. W.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823.
(106) Lauria-Horner Bianca, A.; Pohl Robert, B. *Expert Opin. Invest. Drugs* **2003**, *12*, 663.
(107) Sills, G. J. *Curr. Opin. Pharmacol.* **2006**, *6*, 108.
(108) Silverman, R. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3500.

(109) Lippert, B.; Metcalf, B. W.; Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441.

(110) Jung, M. J.; Palfreyman, M. G. *Vigabatarin in Antiepileptic Drugs*; 4th ed. New York, 1995.

(111) Olpe, H. R.; Demieville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133.

(112) Allan, R. D.; Bates, M. C.; Drew, C. A.; Duke, R. K.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Spence, I. *Tetrahedron* **1990**, *46*, 2511.

(113) Ong, J.; Kerr, D. I. S.; Doolette, D. J.; Duke, R. K.; Mewett, K. N.; Allen, R. D.; Johnston, G. A. R. *Eur. J. Pharmacol.* **1993**, *233*, 169.

(114) Hoekstra, M. S. S., D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrick- son, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Proc. Res. Dev.* **1997**, *1*, 26.

(115) Ordonez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3.

(116) Friestad, G. K.; Banerjee, K. *Org. Lett.* **2009**, *11*, 1095.

(117) Friestad, G. K.; Marie, J.-C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249.

(118) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676.

(119) Levin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(120) Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 8894.

(121) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(122) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(123) Wipf, P.; Takada, T.; Rishel, M. J. *Org. Let.*. **2004**, *6*, 4057.

(124) Pihko, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **1998**, *63*, 92.

(125) Nevalainen, M.; Koskinen, A. M. P. *Synlett* **2001**, *5*, 640.

(126) Pando, O.; Do¨rner, S.; Preusentanz, R.; Denkert, A.; Porzel, A. R., W.; Wessjohann, L. *Org. Lett.* **2009**, *11*, 5567.

(127) Brenner, M.; Seebach, D. *Helv. Chim. Acta* **2001**, 2155.

(128) Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2429.

(129) Jeulin, S.; Ayad, T.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 1592.

(130) Pautigny, C.; Jeulin, S.; Ayad, T.; Zhang, Z.; Genet, J.-P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2008**, *350*, 2525.

(131) Qiu, M.; Wang, D.-Y.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Deng, J.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 210.

(132) Zhao, J.; Burgess, K. *Org. Lett.* **2009**, *11*, 2053.

(133) Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, *9*, 3453.

(134) Hekking, K. F. W.; Lefort, L.; de Vries, A. H. M.; van Delft, F. L.; Schoemaker, H. E.; de Vries, J. G.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2008**, *350*, 85.

(135) Abo, M.; Mori, K. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 265.

(136) Christopfel, W. C.; Vineyard, B. D. *J. Am. Chem. Soc.* **1979**, *101*, 4406.

(137) Schmidt, T.; Baumann, W.; Drexler, H. J.; Heller, D. *J. Organomet. Chem.* **2011**, *696*, 1760.

(138) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977.

(139) Wolff, M.; Seemann, M.; Grosdemange-Billiard, C.; Tritsch, D.; Campos, N.; Rodriguez-Concepcion, M.; Boronat, A.; Rohmer, M. *Tetrahedron Lett.* **2002**, *43*, 2555.

(140) Huang, F.-C.; Lee, L. F. H.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J.; Caspi, E.; Eck, C. R. *J. Am. Chem. Soc.* **1975**, *97*, 4144.

(141) Krohn, K.; Riaz, M.; Floerke, U. *Eur. J. Org. Chem.* **2004**, 1261.

(142) Krohn, K.; Riaz, M. *Tetrahedron Lett.* **2004**, *45*, 293.

(143) Fontana, A. *J. Org. Chem.* **2001**, *66*, 2506.

(144) Cheng, C.; Brookhart, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9422.

(145) Quintard, A.; Alexakis, A.; Mazet, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 2354.

(146) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(147) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

(148) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

(149) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.

(150) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

(151) Yadav, J. S.; Sengupta, S. *Eur. J. Org. Chem.* **2013**, *2013*, 376.

(152) Sawada, D.; Katayama, T.; Tsukuda, Y.; Saito, N.; Saito, H.; Takagi, K.-i.; Ochiai, E.; Ishizuka, S.; Takenouchi, K.; Kittaka, A. *Tetrahedron* **2010**, *66*, 5407.

(153) Mori, K.; Kyota, H.; Malosse, C.; Rochat, D. *Liebigs Ann. Chem.* **1993**, 1201.

(154) Broca, C.; Manteghetti, M.; Gross, R.; Baissac, Y.; Jacob, M.; Petit, P.; Sauvaire, Y.; Ribes, G. *Eur. J. Pharmacol.* **2000**, *390*, 339.

(155) Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355.

(156) Cudic, M.; Mari, F.; Fields, G. B. *J. Org. Chem.* **2007**, *72*, 5581.

(157) Adrian Meredith, J.; Wallberg, H.; Vrang, L.; Oscarson, S.; Parkes, K.; Hallberg, A.; Samuelsson, B. *Eur. J. Med. Chem.* **2010**, *45*, 160.

(158) Mantilli, L.; Gerard, D.; Torche, S.; Besnard, C.; Mazet, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5143.

(159) Mantilli, L.; Mazet, C. *Tetrahedron Lett.* **2009**, *50*, 4141.

(160) Mantilli, L.; Gerard, D.; Torche, S.; Besnard, C.; Mazet, C. *Chem. Eur. J.* **2010**, *16*, 12736.

(161) Mantilli, L.; Mazet, C. *Chem. Commun.* **2010**, *46*, 445.

(162) Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874.

(163) Fantasia, S.; Petersen, J. L.; Jacobsen, H.; Cavallo, L.; Nolan, S. P. *Organometallics* **2007**, *26*, 5880.

(164) Suessner, M.; Plenio, H. *Chem. Commun.* **2005**, 5417.

(165) Poater, A.; Ragone, F.; Giudice, S.; Costabile, C.; Dorta, R.; Nolan, S. P.; Cavallo, L. *Organometallics* **2008**, *27*, 2679.

(166) Burgess, K.; Perry, M. C.; Cui, X. In *New Methodologies in Asymmetric Catalysis*; Malhotra, S., Ed.; ACS Publications: 2003.
(167) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(168) Borguet, Y.; Zaragoza, G.; Demonceau, A.; Delaude, L. *Dalton Trans.* **2013**, *42*, 7287.
(169) Cadu, A.; Andersson, P. G. *J. Organomet. Chem.* **2012**, *714*, 3.
(170) Paczal, A.; Benyei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969.
(171) Hirano, K.; Biju, A. T.; Glorius, F. *J. Org. Chem.* **2009**, *74*, 9570.
(172) Reetz, M. T.; Bondarev, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 4523.
(173) Reetz, M. T.; Guo, H. *Beilstein J. Org. Chem.* **2005**, *1*, No 3.
(174) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2165.
(175) Reetz, M.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 790.
(176) Mrsic, N.; Panella, L.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2011**, *22*, 36.
(177) Mrsic, N.; Panella, L.; Ijpeij, E. G.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *ChemCatChem* **2011**, *3*, 1139.
(178) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4209.
(179) Pena, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087.
(180) Reetz, M. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2556.
(181) Zhang, W.; Zhang, X. *J. Org. Chem.* **2007**, *72*, 1020.
(182) Enthaler, S.; Erre, G.; Junge, K.; Michalik, D.; Spannenberg, A.; Marras, F.; Gladiali, S.; Beller, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1288.
(183) Gennari, C.; Monti, C.; Piarulli, U. *Pure Appl. Chem.* **2006**, *78*, 303.
(184) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.
(185) Xu, Y.-J.; Liu, Q.-Z.; Dong, L. *Synlett* **2007**, 273.
(186) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620.
(187) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374.
(188) Sebesta, R.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2007**, *349*, 1931.
(189) Helmchen, G.; Dahnz, A.; Dubon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.
(190) Van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; De Vries, J. G.; Van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1073.
(191) Bartels, B.; Helmchen, G. *Chem. Comm* **1999**, 741.
(192) Diez-Holz, C. J.; Boeing, C.; Francio, G.; Hoelscher, M.; Leitner, W. *Eur. J. Org. Chem.* **2007**, 2995.

(193) Giancarlo Franciò, F. F., and Walter Leitner *J. Am. Chem. Soc.* **2002**, *124*, 736.
(194) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.
(195) Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8971.
(196) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192.
(197) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2068.
(198) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15249.
(199) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany; Chichester, England, 2003.
(200) Samojlowicz, C.; Grela, K. *ARKIVOC* **2011**, 71.
(201) Wang, Q.-F.; He, W.; Liu, X.-Y.; Chen, H.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron: Asymmetry* **2008**, *19*, 2447.
(202) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(203) Camm, K. D.; Castro, N. M.; Liu, Y.; Czechura, P.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 4168.
(204) Reyes, S. J.; Burgess, K. *Chem. Soc. Rev.* **2006**, *35*, 416.
(205) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem. Int. Ed.* **1996**, *35*, 220.
(206) Burgess, K.; Moye-Sherman, D.; Porte, A. M. In *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds.; ACS: 1996, p 128.
(207) Jandeleit, B.; Turner, H. W.; Uno, T.; vanBeek, J. A. M.; Weinberg, W. H. *CATTECH* **1998**, *2*, 101.
(208) Crabtree, R. H. *Chem. Commun* **1999**, 1611.
(209) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.
(210) Slagt, V. F.; Leeuwen, P. W. N. M. v.; Reek, J. N. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5619.
(211) Slagt, V. F.; Leeuwen, P. W. N. M. v.; Reek, J. N. H. *Chem. Commun.* **2003**, 2474.
(212) Slagt, V.; Roder, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 4056.
(213) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem Soc.* **2004**, *126*, 4494.
(214) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494.
(215) Dydio, P.; Breuil, P.-A. R.; Reek, J. N. H. *Isr. J. Chem.* **2013**, *53*, 61.
(216) Polborn, K.; Severin, K. *Chem. - Eur. J.* **2000**, *6*, 4604.
(217) Polborn, K.; Severin, K. *Eur. J. Inorg. Chem.* **2000**, 1687.
(218) Wulff, G.; Liu, J. *Acc. Chem. Res.* **2012**, *45*, 239.
(219) Carboni, S.; Gennari, C.; Pignataro, L.; Piarulli, U. *Dalton Trans.* **2011**, *40*, 4355.
(220) Sandee, A. J.; Reek, J. N. H. *Dalton Trans.* **2006**, 3385.

(221) Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 6816.
(222) Wilkinson, M. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Org. Biomol. Chem.* **2005**, *3*, 2371.
(223) van Leeuwen, P. W. N. M. *Homogeneous Catalysis: Understanding the Art*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2004.
(224) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2011**, *111*, 2077.
(225) Otto, S.; Severin, K. *Top. Curr. Chem.* **2007**, *277*, 267.
(226) Hamieh, S.; Ludlow, R. F.; Perraud, O.; West, K. R.; Mattia, E.; Otto, S. *Org. Lett.* **2012**, *14*, 5404.
(227) Matsumoto, M.; Nicholas, K. M. *J. Org. Chem.* **2007**, *72*, 9308.
(228) Li, J.; Nowak, P.; Otto, S. *J. Am. Chem. Soc.* **2013**, *135*, 9222.
(229) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652.
(230) Hunt, R. A. R.; Otto, S. *Chem. Commun.* **2011**, *47*, 847.
(231) Gasparini, G.; Vitorge, B.; Scrimin, P.; Jeannerat, D.; Prins, L. J. *Chem. Commun.* **2008**, 3034.
(232) Gasparini, G.; Martin, M.; Prins, L. J.; Scrimin, P. *Chem. Commun.* **2007**, 1340.
(233) Vial, L.; Sanders, J. K. M.; Otto, S. *New J. Chem.* **2005**, *29*, 1001.
(234) Ludlow, R. F.; Liu, J.; Li, H.; Roberts, S. L.; Sanders, J. K. M.; Sijbren, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 5762.
(235) Gasparini, G.; Prins, L. J.; Scrimin, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 2475.
(236) Matsumoto, M.; Estes, D.; Nicholas, K. M. *Eur. J. Inorg. Chem.* **2010**, 1847.
(237) Brisig, B.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1270.
(238) Breuil, P.-A. R.; Patureau, F. W.; Reek, H. N. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2162.
(239) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188.
(240) Moteki, S. A.; Toyama, K.; Liu, Z.; Ma, J.; Holmes, A. E.; Takacs, J. M. *Chem. Commun.* **2012**, *48*, 263.
(241) Wieland, J.; Breit, B. *Nat. Chem.* **2010**, *2*, 832.
(242) Gasparini, G.; Dal Molin, M.; Prins, L. J. *Eur. J. Org. Chem.* **2010**, 2429.
(243) Polborn, K.; Severin, K. *Chem. Commun.* **1999**, 2481.
(244) Meeuwissen, J.; Reek, J. N. H. *Nat. Chem.* **2010**, *2*, 615.
(245) Bian, Z.-Y.; Sumi, K.; Furue, M.; Sato, S.; Koike, K.; Ishitani, O. *J. Chem. Soc., Dalton Trans.* **2009**, 983.
(246) Santamaria, J.; Jroundi, R. *Tetrahedron Lett.* **1991**, *32*, 4291.
(247) Irie, R.; Masutani, K.; Katsuki, T. *Synlett* **2000**, 1433.
(248) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166.
(249) Osawa, M.; Nagai, H.; Akita, M. *J. Chem. Soc., Dalton Trans.* **2007**, 827.

(250) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.
(251) Rau, S.; Walther, D.; Vos, J. G. *J. Chem. Soc., Dalton Trans.* **2007**, 915.
(252) Imperato, G.; Koenig, B. *ChemSusChem* **2008**, *1*, 993.
(253) Inagaki, A.; Edure, S.; Yatsuda, S.; Akita, M. *Chem. Commun.* **2005**, 5468.
(254) Inagaki, A.; Yatsuda, S.; Edure, S.; Suzuki, A.; Takahashi, T.; Akita, M. *Inorg. Chem.* **2007**, *46*, 2432.
(255) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456.
(256) Bures, F.; Szotkowski, T.; Kulhanek, J.; Pytela, O.; Ludwig, M.; Holcapek, M. *Tetrahedron: Asymmetry* **2006**, *17*, 900.
(257) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740.
(258) Kotsuki, H.; Hayakawa, H.; Wakao, M.; Shimanouchi, T.; Ochi, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2665.
(259) Perl, N. R.; Leighton, J. L. *Org. Lett.* **2007**, *9*, 3699.
(260) Shitama, H.; Katsuki, T. *Chem. - Eur. J.* **2007**, *13*, 4849.
(261) Gullotti, M.; Santagostini, L.; Pagliarin, R.; Granata, A.; Casella, L. *J. Mol. Catal. A Chem.* **2005**, *235*, 271.
(262) Hodgson, R.; Douthwaite, R. E. *J. Organomet. Chem.* **2005**, *690*, 5822.
(263) Kamlet, A. S.; Neumann, C. N.; Lee, E.; Carlin, S. M.; Moseley, C. K.; Stephenson, N.; Hooker, J. M.; Ritter, T. *PLoS One* **2013**, *8*, 1.
(264) Stenhagen Ida, S. R.; Kirjavainen Anna, K.; Forsback Sarita, J.; Jorgensen Charlotte, G.; Robins Edward, G.; Luthra Sajinder, K.; Solin, O.; Gouverneur, V. *Chem Commun (Camb)* **2013**, *49*, 1386.
(265) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, *2008*, 3707.
(266) Smith, A. M. I.; Beiger, J. J.; Davulcu, A. H.; Cox, J. M. *Org. Synth.* **2005**, *82*, 147.
(267) Fujii, T.; Ohba, M.; Sakari, M. *Heterocycles* **1988**, *27*, 2077.
(268) Sherrill, R. G.; Andrews, C. W.; Bock, W. J.; Davis-Ward, R. G.; Furfine, E. S.; Hazen, R. J.; Rutkowske, R. D.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 81.
(269) Diez, S.; Navarro, G.; Tros de Ilarduya, C. *J. Gene Med.* **2009**, *11*, 38.
(270) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496.

APPENDIX A
GENERAL EXPERIMENTAL PROCEDURES

A. General Methods

All reactions were carried out under an atmosphere of dry nitrogen or argon. Glassware was oven-dried prior to use. Unless otherwise indicted, common reagents or materials were obtained from commercial source and used without further purification. All the solvents were used after appropriate distillation or purification.

Flash column chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Optical rotations were measured on Jasco DIP-360 digital polarimeter. ^{1}H and ^{13}C spectra were recorded on Varian 300 (300 MHz ^{1}H; 75 MHz ^{13}C), Avance 400 (400 MHz ^{1}H; 100 MHz ^{13}C) or Varian 500 (500 MHz ^{1}H; 125 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual $CDCl_3$ (δ 7.28 ppm ^{1}H; δ 77.0 ppm ^{13}C), CD_3OD (δ 3.31 ppm ^{1}H; δ 49.0 ppm ^{13}C) or d^6-DMSO (δ 2.49 ppm ^{1}H; δ 39.5 ppm ^{13}C). Coupling constants (J) were reported in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dq = double quartet m = multiplet, br = broad.

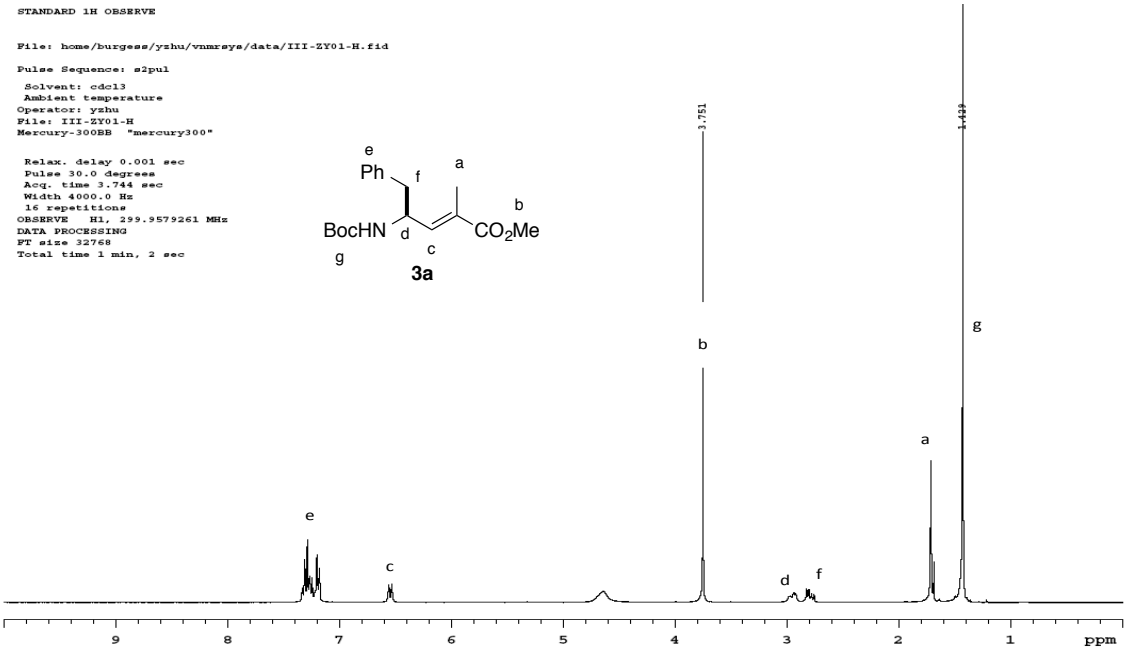
APPENDIX B
EXPERIMENTAL FOR CHAPTER II

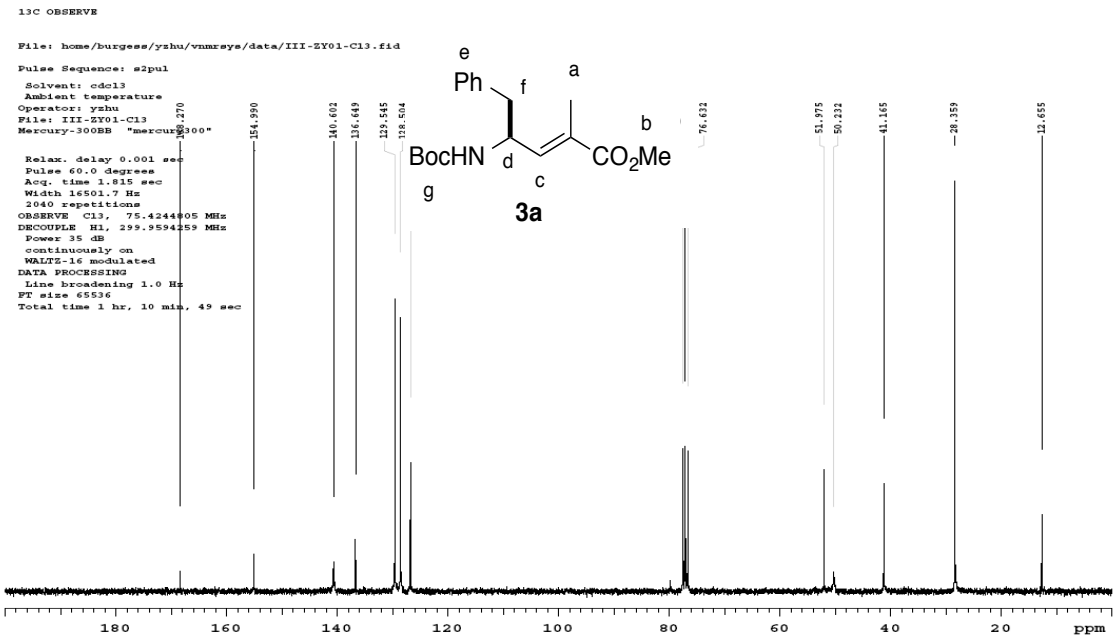
A. Preparation of compounds 3 – 11.

Synthesis Of α-Methyl-γ-Amino Acid Derivatives 3.

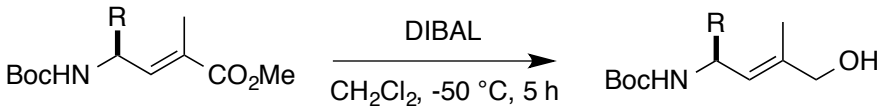
α-Methyl-γ-amino acid alkene-derivatives **(*E*-3)** and **(*Z*-3)** were synthesized via a known procedure.[122,124,265-268]

(*S*)-*E*-Methyl 4-((*tert*-butoxycarbonyl)amino)-2-methyl-5-phenylpent-2-enoate (*E*-3a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.08 (5H, m), 6.56 (1H, d, J = 12 Hz), 4.72-4.54 (2H, br), 3.75 (3H, s), 2.98 (1H, dd, J = 6.0, 14 Hz), 2.79 (1H, dd, J = 12, 18 Hz), 1.71 (3H, d, J = 1.1 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.0, 137.9, 129.9, 128.5, 126.6, 125.0, 79.9, 52.2, 50.4, 41.4, 28.6, 12.9. HRMS (ESI): Exact mass calcd for $C_{18}H_{25}LiNO_4$ *ie* $[M+Li]^+$ 326.1944. Found 326.2052.





General Procedure For Syntheses Of Compounds (*E*)-4, Illustrated For 4a



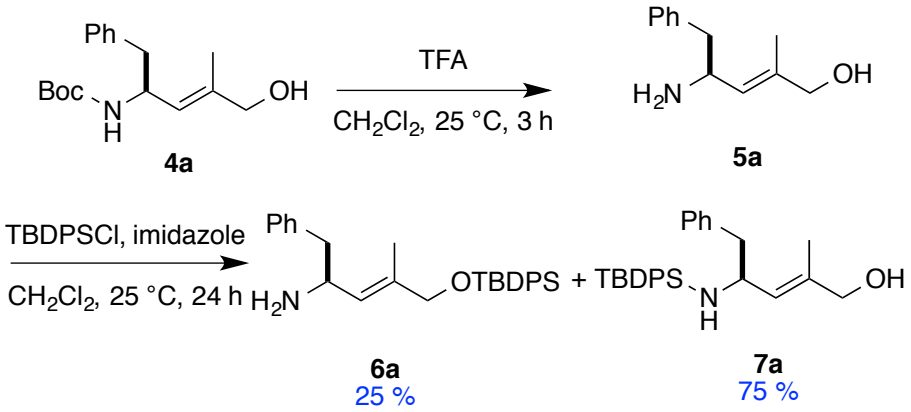
3 **4**

R = Bn, **a**; Me, **b**; ^{i}Pr, **c**; CH_2OBn, **d**; $CH_2(4\text{-}BnOC_6H_4\text{-})$, **e**.

The phenylalanine derivative **3a** (0.9 g, 2.7 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to -50 ^{o}C. A DIBAL solution (1M in hexane) (8.1 mL, 8.1 mmol) was added slowly, then the reaction was stirred at -50 ^{o}C for 5 h and then quenched by addition of EtOAc (0.5 mL). Saturated potassium sodium tartrate solution (20 mL) was added, and the mixture was warmed to 25 ^{o}C and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 30% EtOAc/hexanes as eluent

giving **(*S*)-*E*-*tert*-butyl (5-hydroxy-4-methyl-1-phenylpent-3-en-2-yl)carbamate (4a)** as a colorless oil (0.7 g, 2.4 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (5H, m), 5.31 (1H, dq, *J* = 1.5, 9.0 Hz), 4.55 (2H, br), 3.97 (2H, s), 2.94 (1H, dd, *J* = 6.0, 13 Hz), 2.73 (1H, dd, *J* = 7.2, 13 Hz), 1.51 (3H, d, *J* = 1.5 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.0, 137.9, 129.9, 128.5, 126.6, 125.0, 79.6, 76.9, 68.1, 50.0, 42.3, 28.7, 14.2. HRMS (ESI): Exact mass calcd for $C_{17}H_{25}NNaO_3$ *ie* $[M+Na]^+$ 314.1732. Found 314.1768.

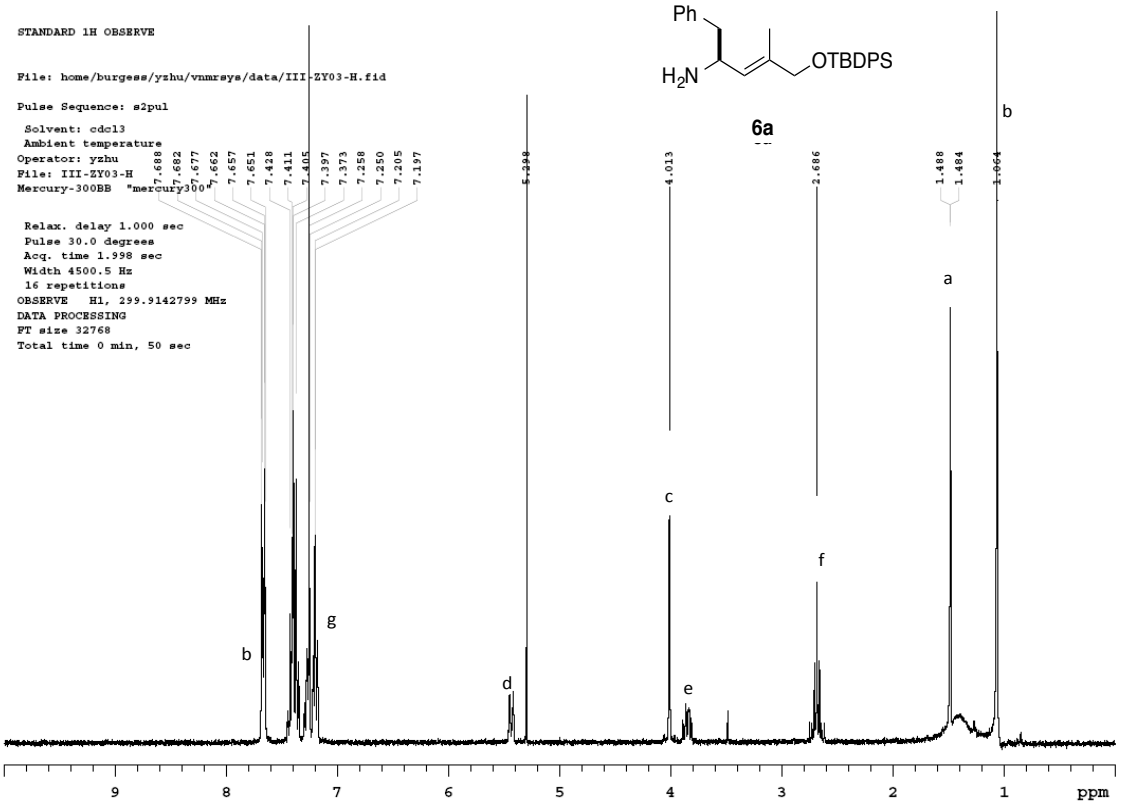
Synthesis Of The Phenylalanine Derivative (*E*)-5a

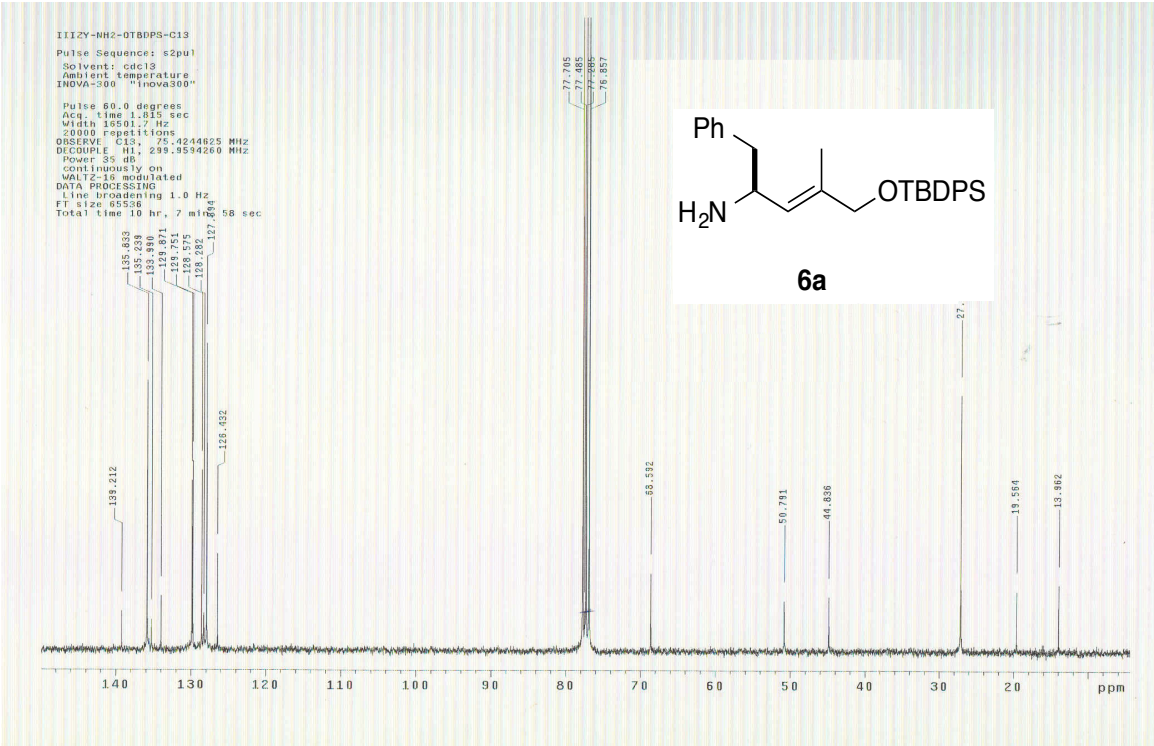


The Boc-protected allylamine **4a** (1.4 g, 4.9 mmol) was dissolved in 30 mL CH_2Cl_2 and cooled to 0 °C. Trifluoroacetic acid (25 mL) was added in one portion, then the mixture was warmed to 25 °C and stirred for 3 h. Solvent was evaporated under a stream of nitrogen, and the residue was dissolved in 20 mL CH_2Cl_2 and washed with 20 mL saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed *in vacuo*. The residue **5a** was used without further purification.

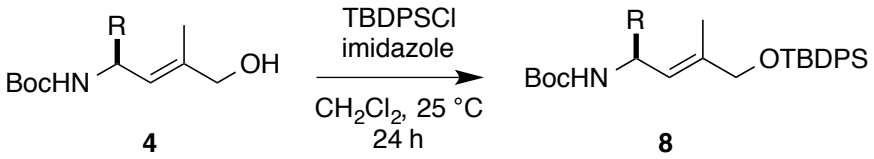
Allylic amine **5a** was dissolved in CH_2Cl_2 (20 mL) and imidazole (1.2 eq) was then added. *tert*-Butyldiphenylsilyl chloride (1.1 eq) was then added slowly and the resulting mixture was stirred for 1 h at 25 °C. The reaction was quenched with saturated $NaHCO_3$ 20 mL and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The

combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 5% MeOH/CH_2Cl_2 to give 25% of compound **6a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (4H, m), 7.43-7.34 (5H, m), 7.30-7.18 (6H, m), 5.43 (1H, dd, J = 1.2, 8.8 Hz), 5.30 (1H, s), 4.01 (2H, s), 3.06 (1H, m), 2.69 (2H, t, J = 6.3 Hz), 1.48 (3H, d, J = 0.9 Hz), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 135.8, 135.2, 134.0, 129.9, 129.8, 128.6, 128.3, 127.9, 126.4, 68.6, 50.8, 44.8, 27.1, 19.6, 14.0. HRMS (ESI): Exact mass calcd for $C_{28}H_{36}NOSi$ *ie* $[M+H]^+$ 430.2566. Found 430.2502.





General Procedure For Syntheses Of Compounds (*E*)-8, Illustrated For 8a

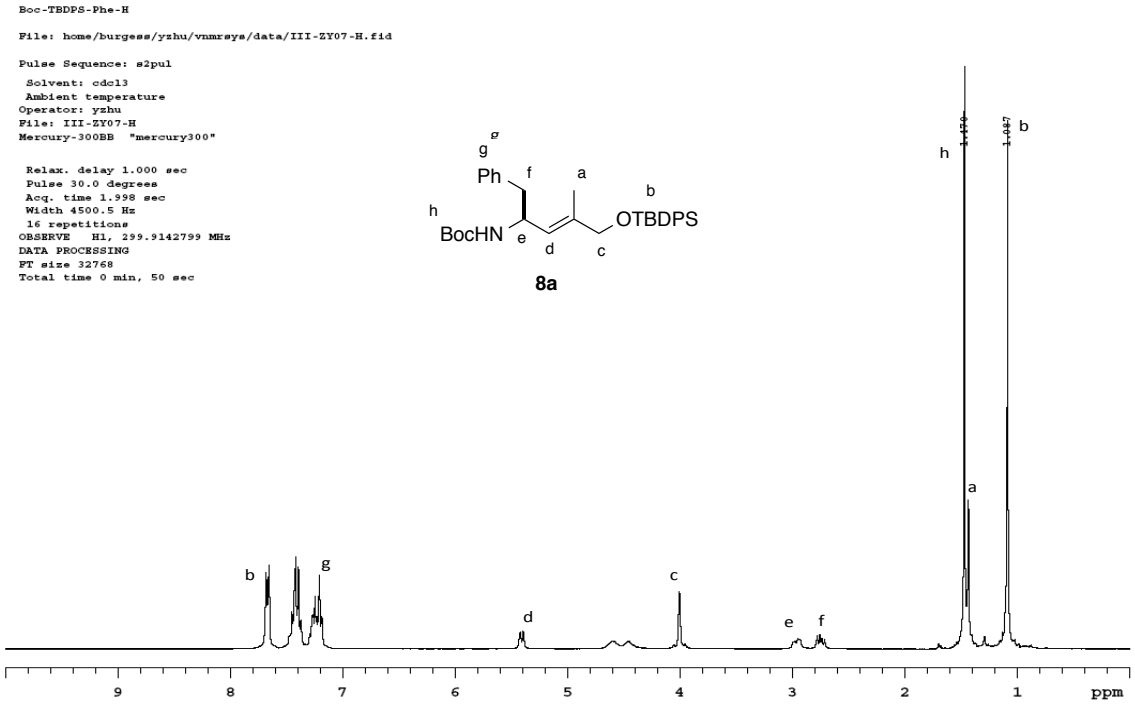


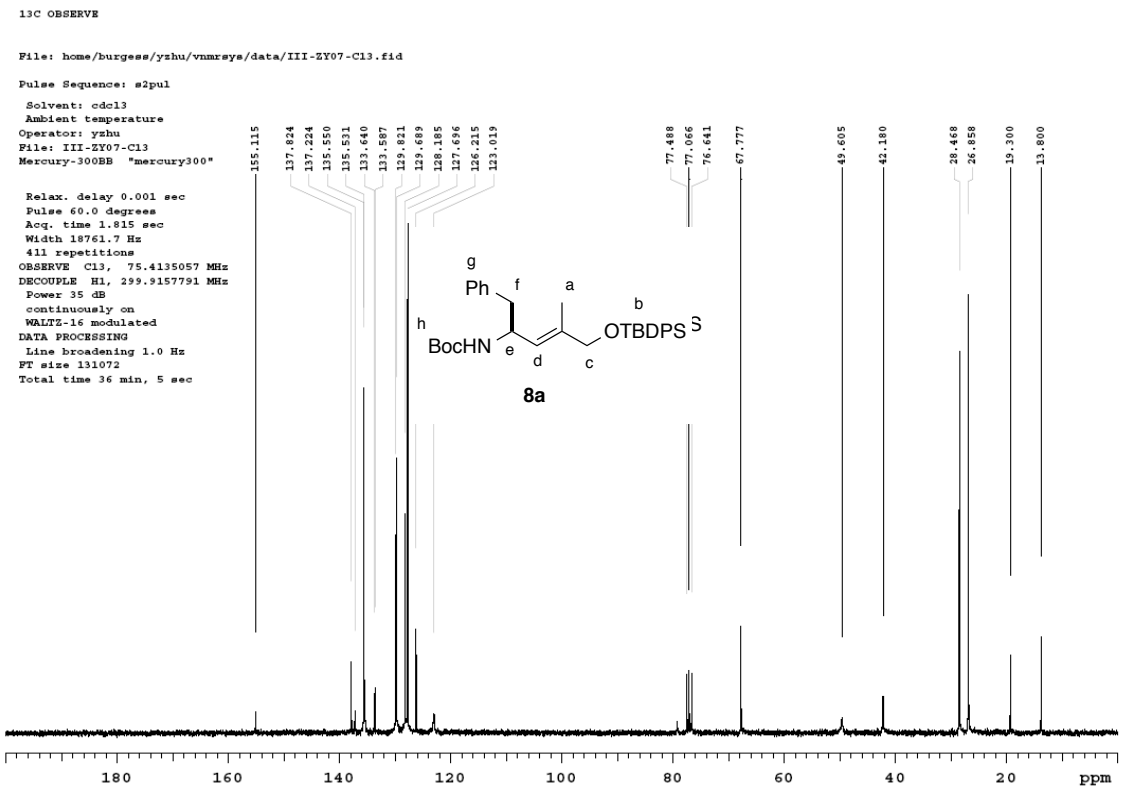
4 **8**

R = Bn, **a**; Me, **b**; ^{i}Pr, **c**; CH_2OBn, **d**; $CH_2(4\text{-}BnOC_6H_4\text{-})$, **e**.

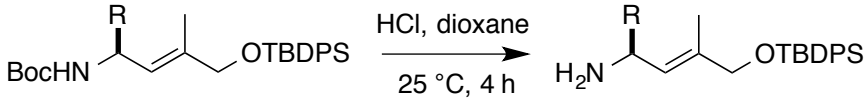
Imidazole (0.7 g, 10 mmol) was added to a stirred solution of Boc-protected allylic amine **4a** (2.7 g, 9.4 mmol) in CH_2Cl_2 (20 mL). *tert*-Butyldiphenylsilyl chloride (2.5 mL, 9.9 mmol) was then added slowly and the resulting mixture was stirred for 24 h. Water (30 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted using CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 10% EtOAc/hexanes as eluent giving **(*S*)-*E*-*tert*-butyl (5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)carbamate (8a)** (4.1 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.66 (4H, m), 7.48-7.37 (6H,

m), 7.29-7.19 (5H, m), 5.41 (1H, d, J = 9.3 Hz), 4.72-4.50 (1H, br), 4.50-4.39 (1H, br), 4.01 (2H, s), 3.05-2.90 (1H, m), 2.75 (1H, dd, J = 7.5, 13 Hz), 1.47 (9H, s), 1.44 (3H, s), 1.09 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 137.8, 137.2, 135.6, 135.5, 133.6 (2 peaks), 129.8, 129.7, 128.2, 127.7, 126.2, 123.0, 79.2, 67.8, 49.6, 42.2, 28.5, 26.9, 19.3, 13.8. HRMS (ESI): Exact mass calcd for $C_{33}H_{43}LiNO_3Si$ *ie* $[M+Li]^+$ 536.3172. Found 536.3175.





General Procedure For Syntheses Of Compounds (*E*)-6, Illustrated For 6a



8

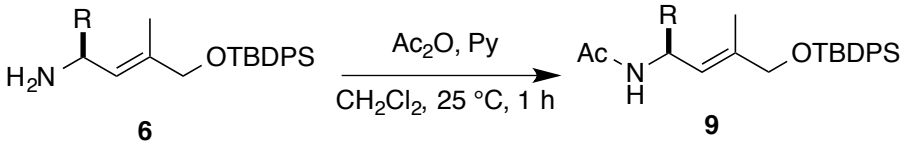
6

R = Bn, **a**; Me, **b**; ^{i}Pr, **c**; CH_2OBn, **d**; $CH_2(4\text{-}BnOC_6H_4\text{-})$, **e**.

A dioxane solution of 4M HCl (3.0 mL, 12 mmol) was added to the Boc-protected amine **8a** (0.5 g, 1.0 mmol) in Et_2O 30 mL, and stirred at 25 ^{o}C for 4 h. The mixture was made basic by additioning of a 10% NaOH solution and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The product **9a** was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (4H, m), 7.43-7.34 (6H, m), 7.30-7.18 (5H, m), 5.43 (1H, dd, *J* = 1.2, 8.8 Hz), 5.30 (1H, s), 4.01 (2H, s), 3.87 (1H, q), 2.69 (2H, t, *J* = 6.3 Hz), 1.52-1.31 (1H, br), 1.48 (3H, d, *J* = 0.9

Hz), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 136.6, 135.8, 135.7, 133.7, 133.6, 130.1, 129.9, 128.8, 128.0, 127.1, 120.4, 68.6, 50.8, 44.8, 27.1, 19.6, 14.0. HRMS (ESI): Exact mass calcd for $C_{28}H_{36}NOSi$ *ie* $[M+H]^+$ 430.2566. Found 430.2502.

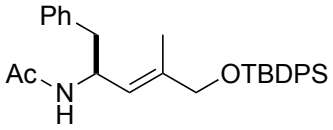
General Procedure For Syntheses Of Allylic Acetates (*E*)-9



6 **9**

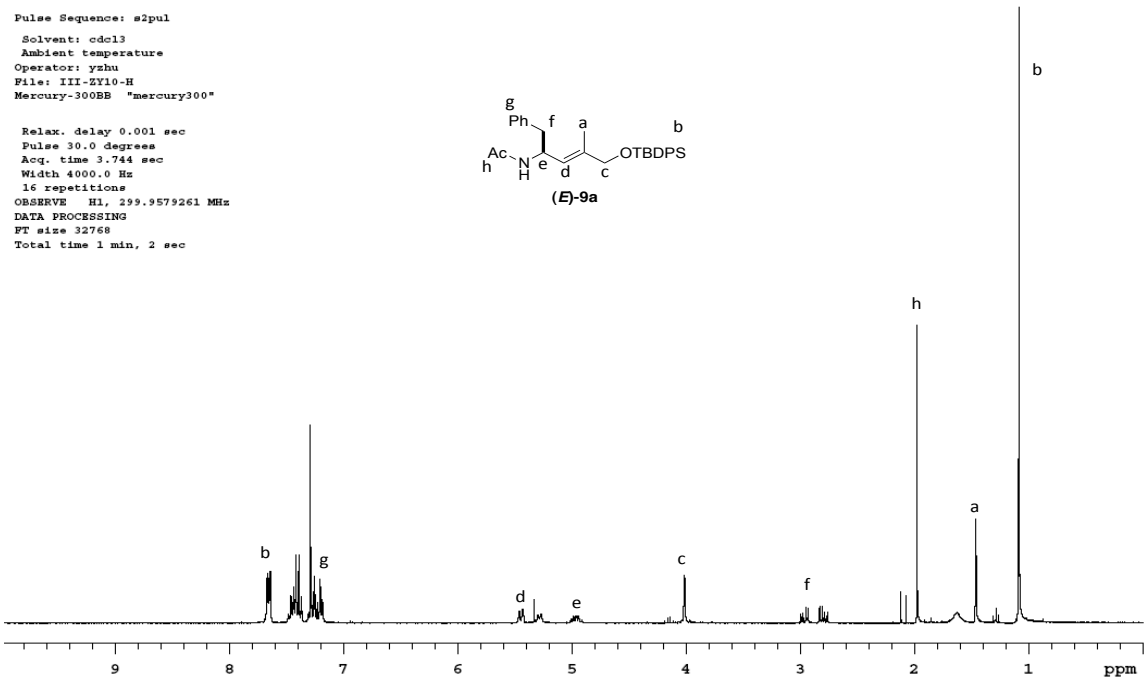
R = Bn, **a**; Me, **b**; ^{i}Pr, **c**; CH_2OBn, **d**; $CH_2(4\text{-}BnOC_6H_4\text{-})$, **e**.

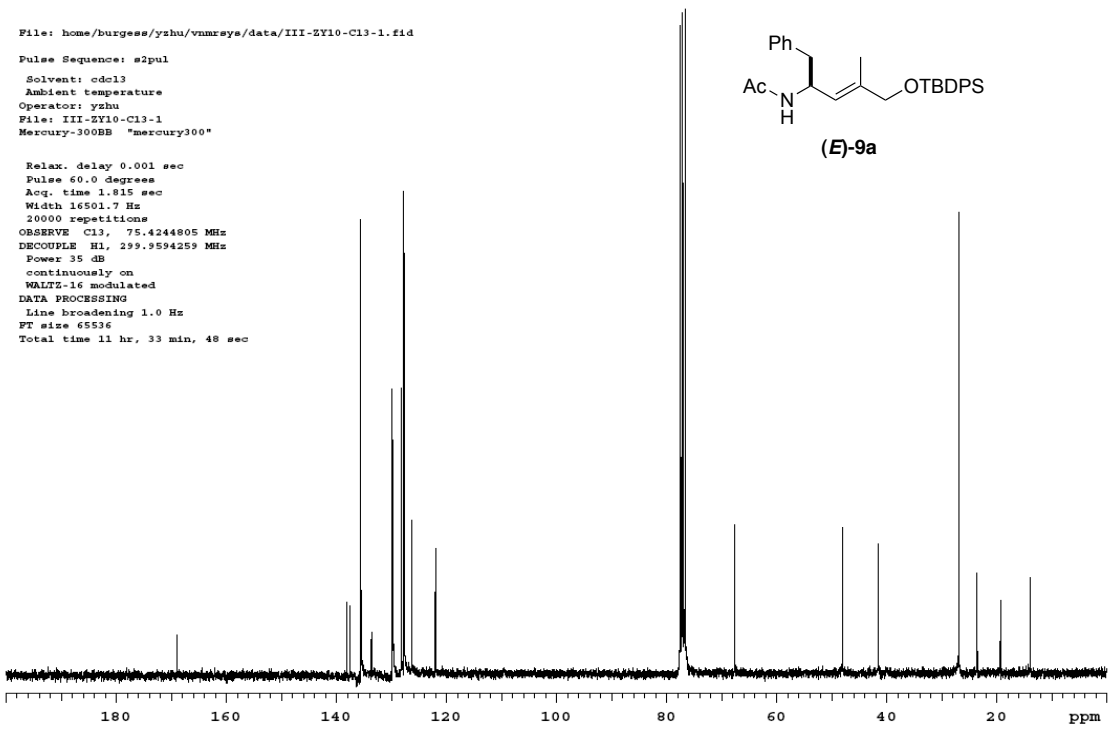
Allylic amine **6** was dissolved in CH_2Cl_2 (0.1M) and pyridine (1.5 eq) was added to the solution. Acetic anhydride (1.1 eq) was added and the mixture was stirred at 25 ^{o}C for 1 h. The solution was washed with 1M HCl(aq) (10 mL), saturated $NaHCO_3$(aq) (10 mL) and water (10 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 50% EtOAc/hexanes as eluent.

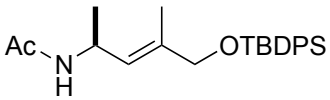


(***E*)-9a**

(*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)acetamide (*E*-9a). Product was obtained as a colorless oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (4H, m), 7.48-7.36 (6H, m), 7.30-7.17 (5H, m), 5.44 (1H, dd, J = 1.5, 9.0 Hz), 5.26 (1H, d), 5.01-4.90 (1H, m), 4.01 (2H, s), 2.96 (1H, dd, J = 4.8, 13 Hz), 2.79 (1H, dd, J = 7.5, 13 Hz), 1.97 (3H, s), 1.28 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 138.3, 137.8, 135.7, 133.9, 133.7, 130.1, 129.9, 128.5, 127.9, 126.5, 122.2, 67.8, 48.2, 41.7, 27.1, 23.7, 19.5, 14.1. HRMS (ESI): Exact mass calcd for $C_{30}H_{38}NO_2Si$ *ie* $[M+H]^+$ 472.2672. Found 472.2666.

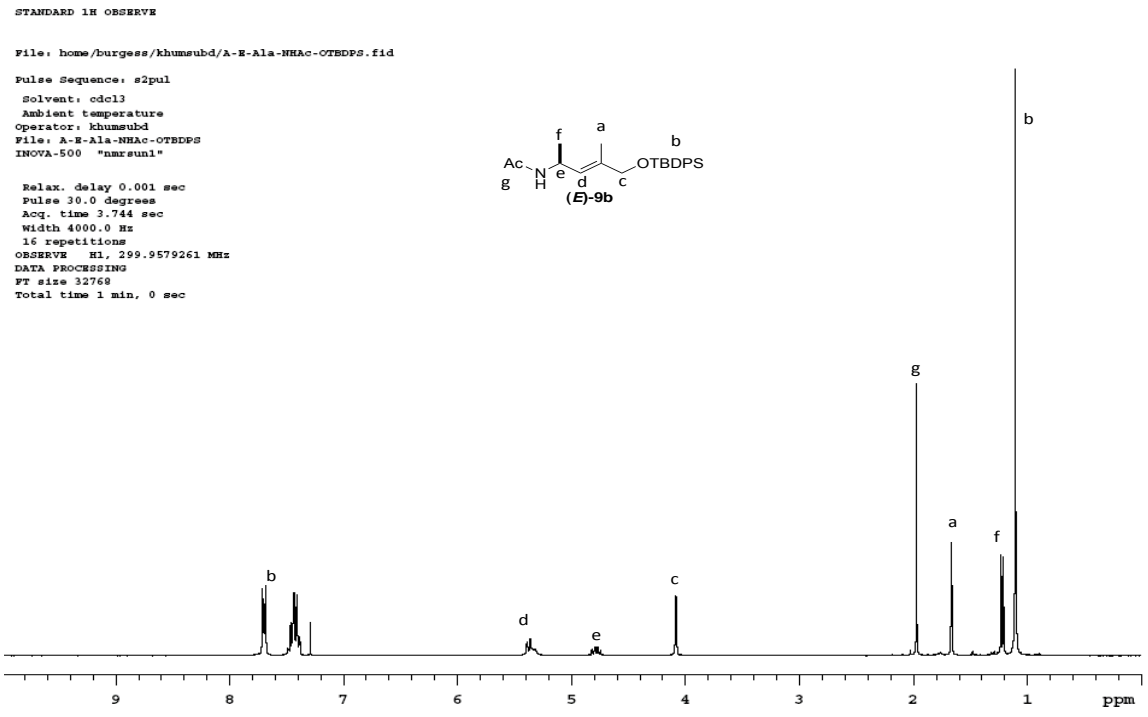

STANDARD 1H OBSERVE
File: home/burgess/yzhu/vnmrsys/data/III-ZY10-H.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: yzhu
File: III-ZY10-H
Mercury-300BB "mercury300"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9579261 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 2 sec
(E)-9a
ppm

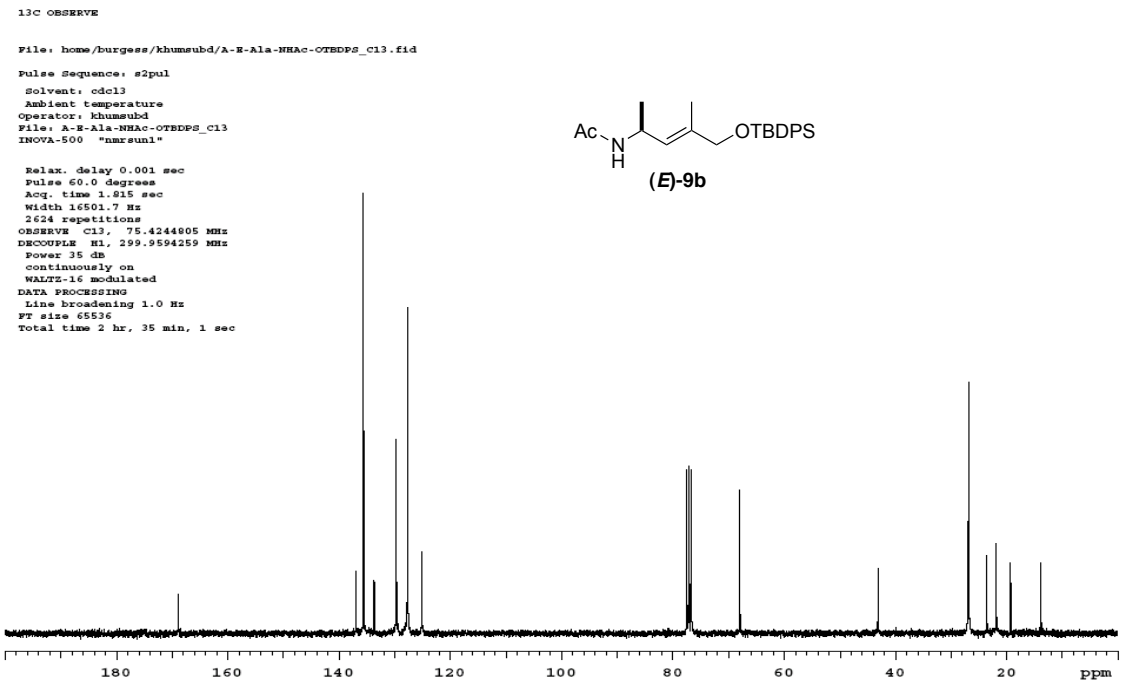

13C OBSERVE
File: home/burgess/yzhu/vnmrsys/data/III-ZY10-C13-1.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: yzhu
File: III-ZY10-C13-1
Mercury-300BB "mercury300"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
20000 repetitions
OBSERVE C13, 75.4244805 MHz
DECOUPLE H1, 299.9594259 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 11 hr, 33 min, 48 sec
(E)-9a
ppm



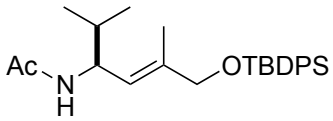
(***E***)-9b

(*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*E*-9b). Product was obtained as a colorless oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (4H, m), 7.47-7.39 (6H, m), 5.40-5.38 (2H, m), 4.82-4.72 (1H, m), 4.08 (2H, s), 1.97 (3H, s), 1.66 (3H, s), 1.22 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 136.9, 135.6, 133.7, 133.6, 129.7, 127.7, 125.1, 68.0, 43.1, 26.9, 23.6, 21.9, 19.3, 13.9. HRMS (ESI): Exact mass calcd for $C_{24}H_{34}NO_2Si$ *ie* $[M+H]^+$ 396.2359. Found 396.2570.





(*E*)-9b



(*E*)-9c

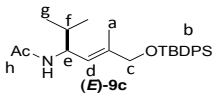
(*S*)-*E*-*N*-(6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhex-4-en-3-yl)acetamide (*E*-9c). Product was obtained as a colorless oil (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.63 (4H, m), 7.42-7.28 (6H, m), 5.42 (1H, d, *J* = 6.0 Hz), 5.22 (1H, d, *J* = 6.0 Hz), 4.59-4.45 (1H, m), 4.07 (2H, s), 1.97 (3H, s), 1.83-1.70 (1H, m), 1.63 (3H, s), 1.07 (9H, s) 0.89 (6H, dd, *J* = 6.3, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 138.3, 135.5 (2 peaks), 133.7, 133.6, 129.7, 127.7, 121.5, 67.9, 51.9, 32.9, 26.8, 23.6, 19.3, 18.7, 18.1, 14.2. HRMS (ESI): Exact mass calcd for $C_{26}H_{38}NO_2Si$ *ie* $[M+H]^+$ 424.2672. Found 424.2682.

STANDARD 1H OBSERVE

File: home/burgess/khumsubd/A-E-Val-NHAc-OTBDPS.fid

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-E-Val-NHAc-OTBDPS
INOVA-500 "nmrsun1"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 299.9142799 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 48 sec



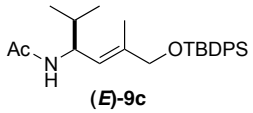
(*E*)-9c

13C OBSERVE

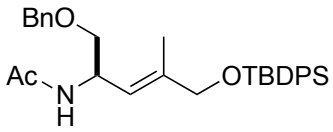
File: home/burgess/khumsubd/A-E-Val-NHAc-OTBDPS_C13.fid

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-E-Val-NHAc-OTBDPS_C13
INOVA-500 "nmrsun1"

Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
16384 repetitions
OBSERVE C13, 75.4135057 MHz
DECOUPLE H1, 299.9157791 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 8 hr, 18 min, 20 sec

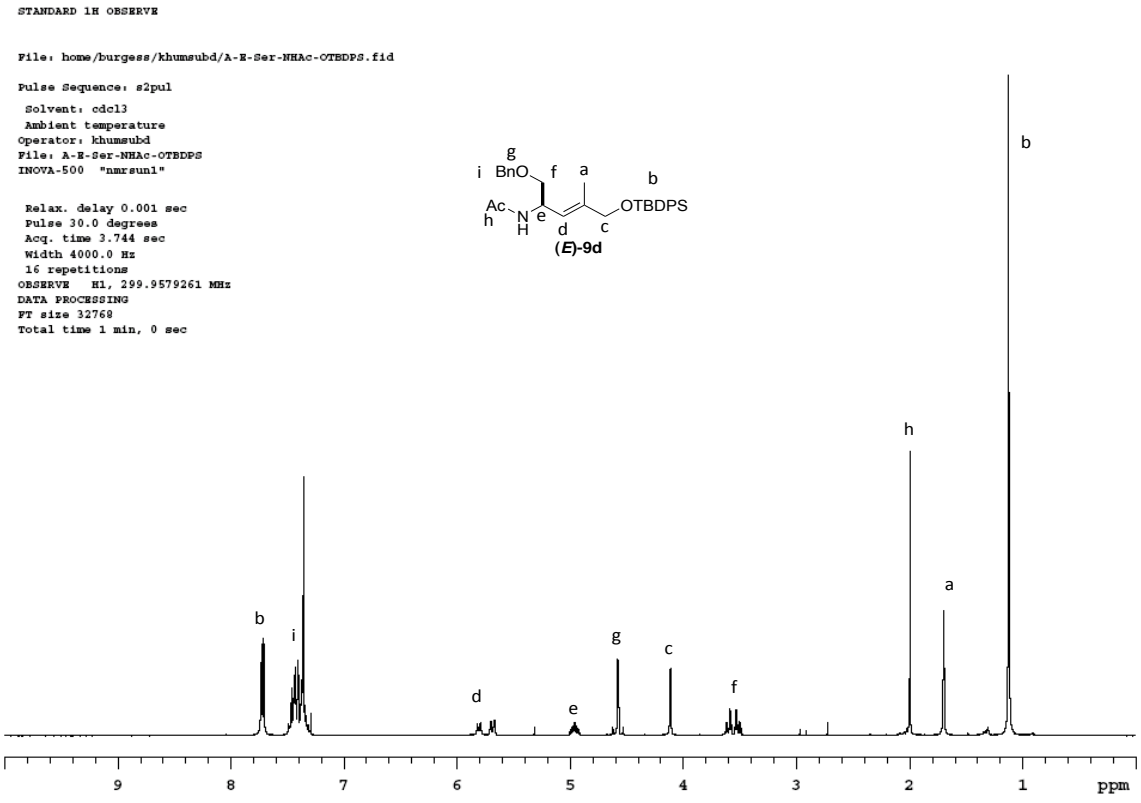


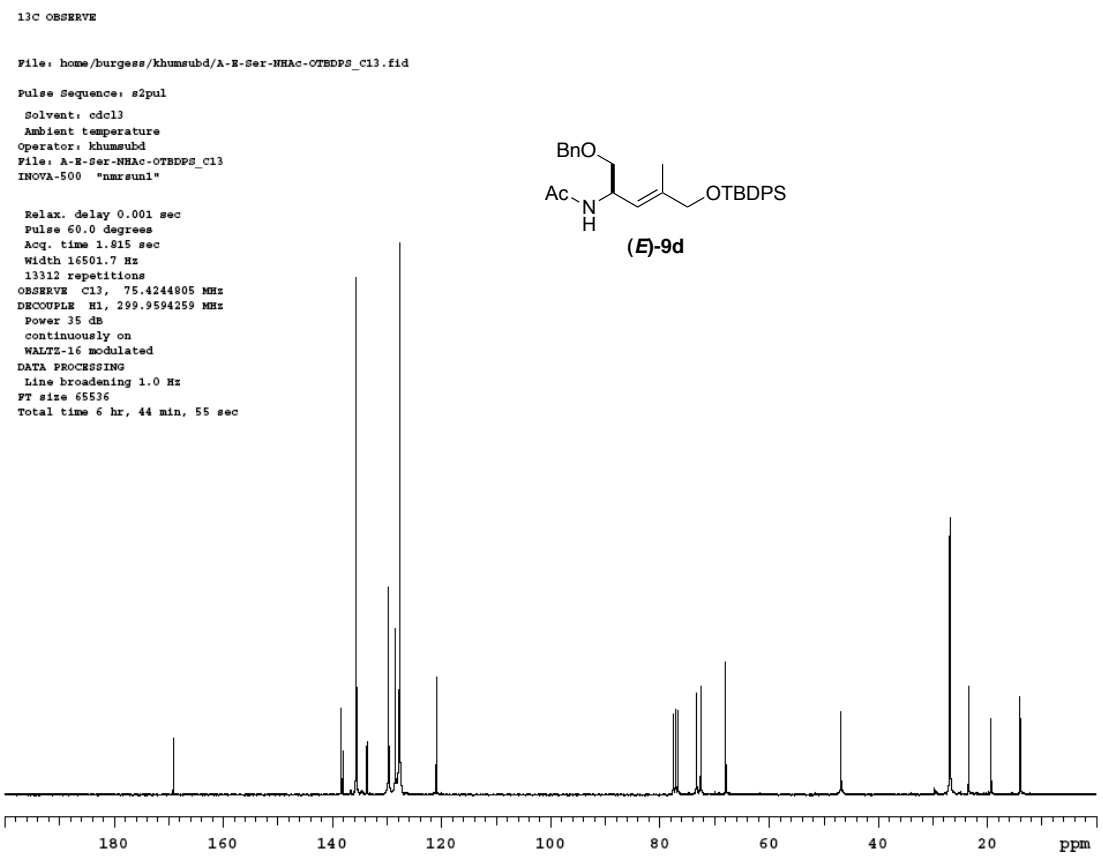
(*E*)-9c

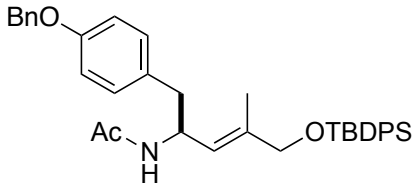


(***E***)-9d

(*R*)-*E*-*N*-(1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*E*-9d). Product was obtained as a colorless oil (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.70 (4H, m), 7.44-7.36 (11H, m), 5.82 (1H, d, *J* = 7.5 Hz), 5.69 (1H, dd, *J* = 3.0, 15 Hz), 5.05-4.92 (1H, m), 4.58 (2H, d, *J* = 2.7 Hz), 4.11 (2H, s), 3.60 (1H, dd, *J* = 5.0, 7.5 Hz), 3.52 (1H, dd, *J* = 5.0, 8.4 Hz), 2.00 (3H, s), 1.70 (3H, s), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 138.4, 138.1, 135.6, 133.7, 133.6, 129.7, 128.5, 128.2, 127.7, 73.3, 72.5, 68.0, 46.9, 26.9, 23.5, 19.3, 14.0. HRMS (ESI): Exact mass calcd for $C_{31}H_{40}NO_3Si$ *ie* $[M+H]^+$ 502.2777. Found 502.2801.



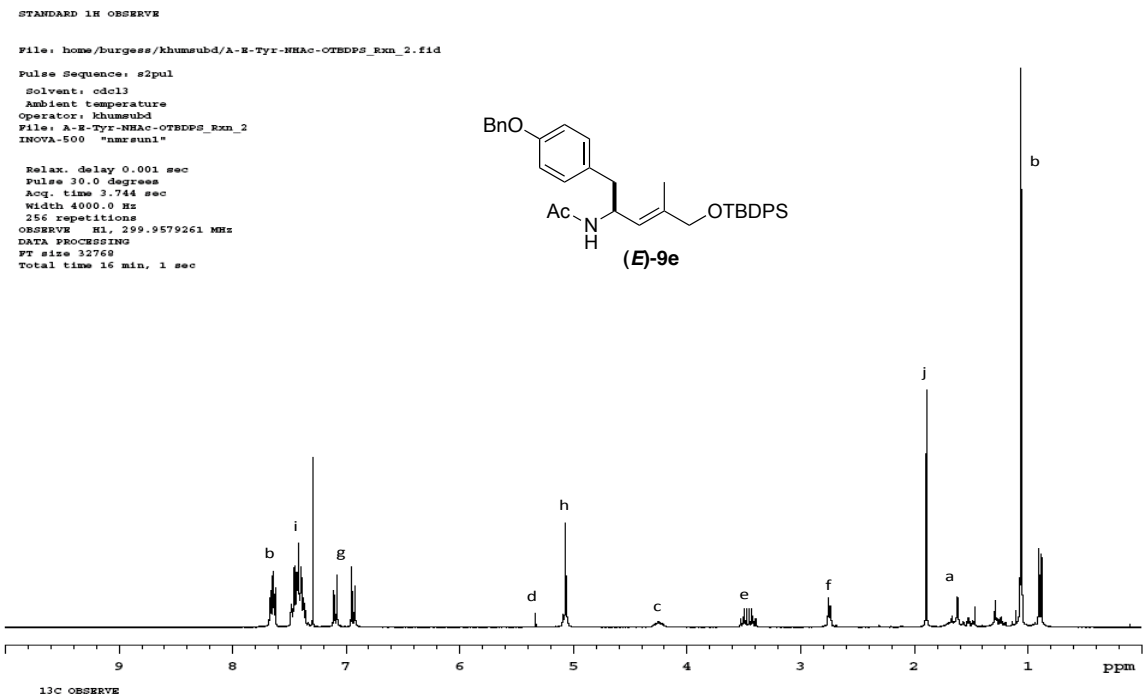


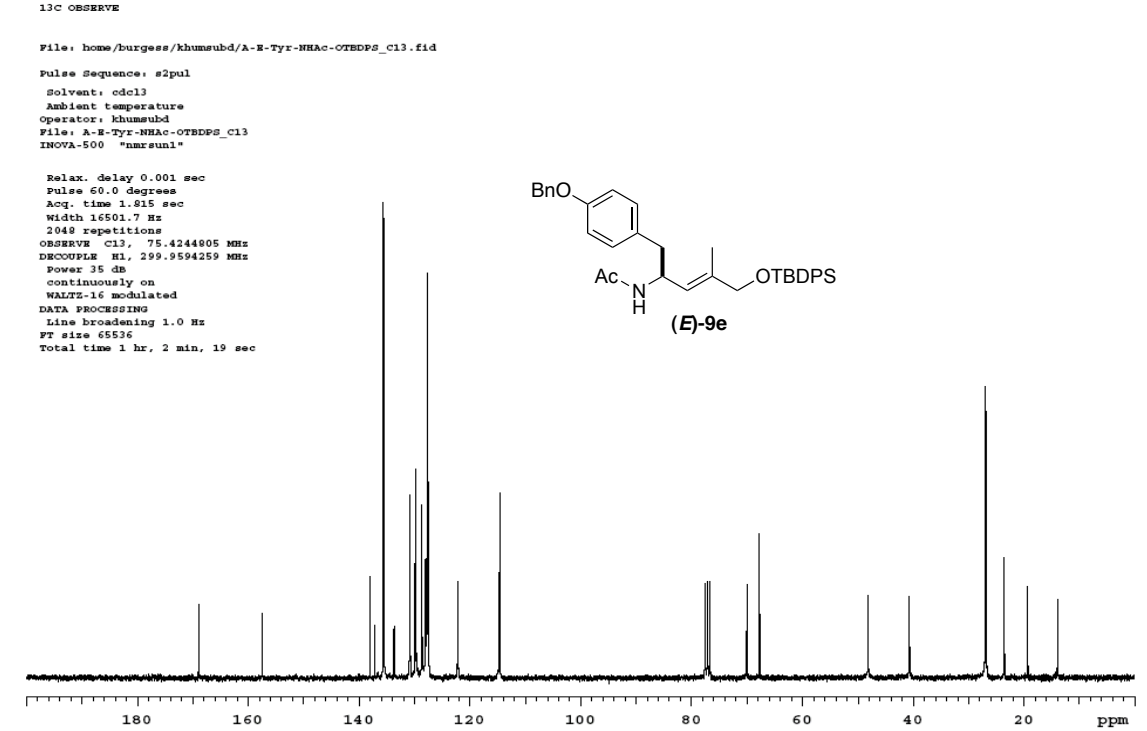


(*E*)-9e

(*S*)-*E*-*N*-(1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*E*-9e). Product was obtained as a colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.67 (4H, m), 7.48-7.40 (11H, m), 7.12 (2H, dd, *J* = 13 Hz), 6.92 (2H, d, *J* = 8.0 Hz), 5.47 (1H, d, *J* = 0.9 Hz), 5.39 (1H, d, *J* = 6.0 Hz), 5.07 (2H, s), 5.01-4.89 (1H, m), 4.05 (2H, s), 2.92 (1H, dd, *J* = 3.0, 12 Hz), 2.85 (1H, dd, *J* = 0.9, 9.0 Hz), 2.00 (3H, s), 1.49 (3H, s), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 157.4, 138.0, 137.2, 135.6, 133.7, 133.5, 130.8, 130.0, 129.7, 128.6, 128.0, 127.7, 127.5, 122.2,

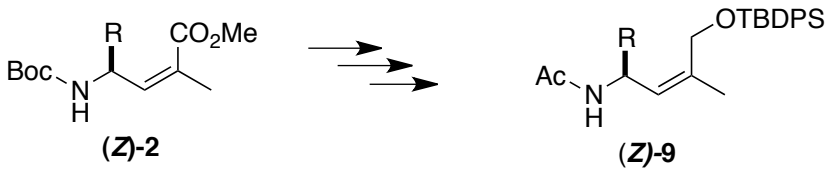
114.7, 70.0, 67.7, 48.2, 40.7, 26.9, 23.5, 19.3, 14.0. HRMS (ESI): Exact mass calcd for $C_{37}H_{44}NO_3Si$ *ie* $[M+H]^+$ 578.3090. Found 578.3075.





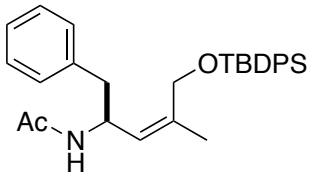
Synthesis Of (*Z*)-9

(*Z*)-9 was synthesized from **(*Z*)-2** by using the same procedure for synthesis of compounds **(*E*)-9.**



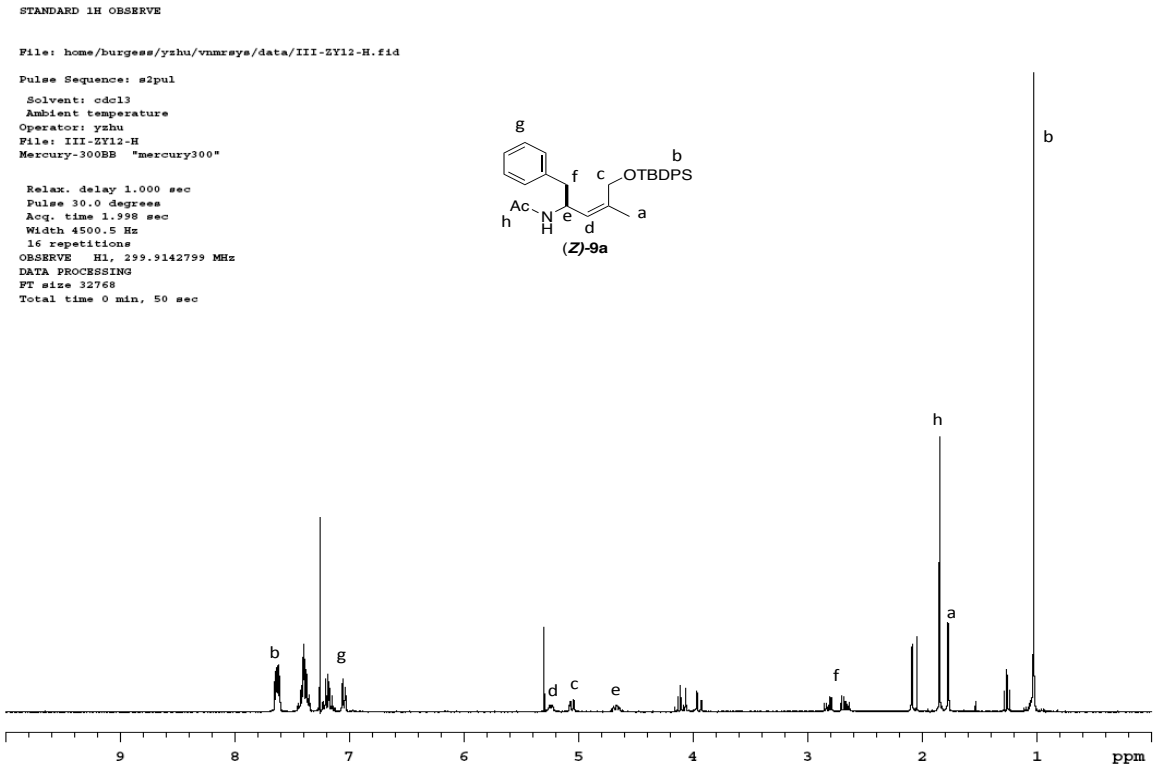
(*Z*)-2 (*Z*)-9

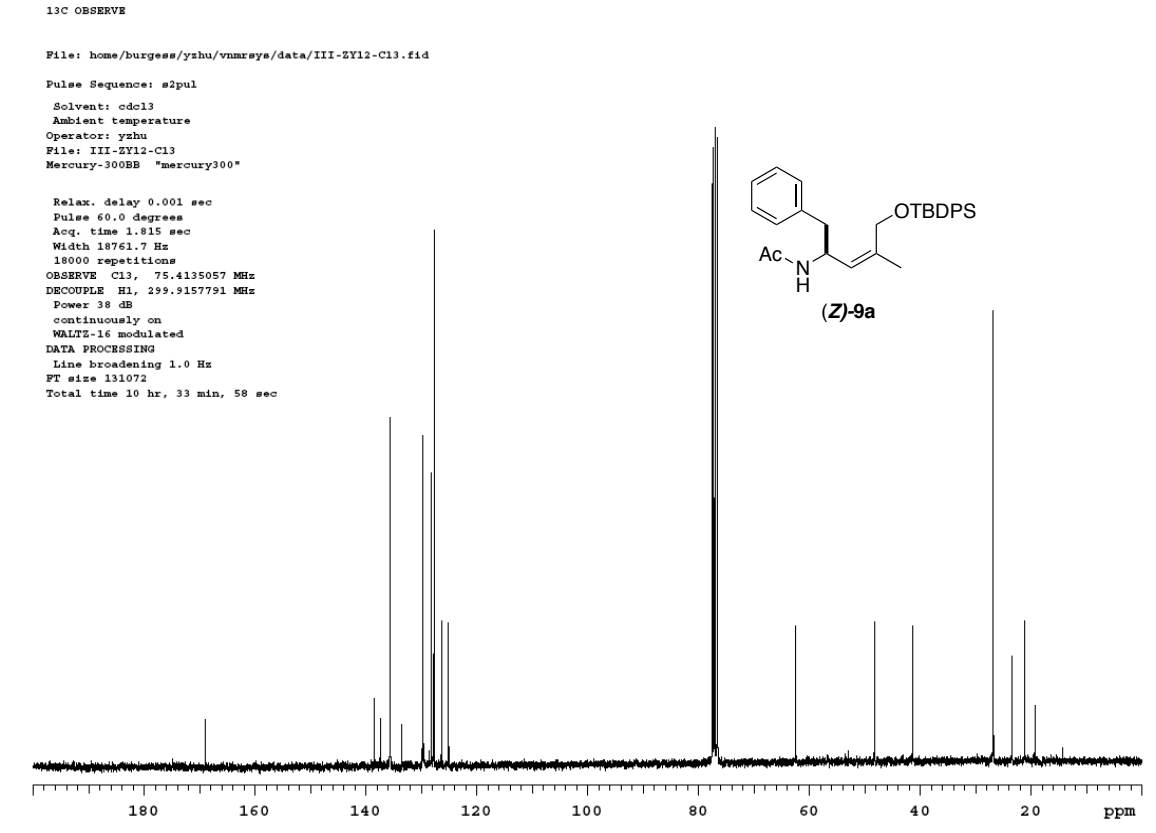
R = Bn, **a**; Me, **b**; ^{i}Pr, **c**; CH_2OBn, **d**; $CH_2(4\text{-}BnOC_6H_4\text{-})$, **e**.

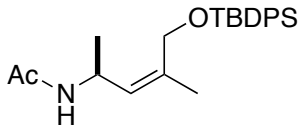


(*Z*)-9a

(*S*)-*Z*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)acetamide (*Z*-9a). Product was obtained as a colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (4H, m), 7.45-7.37 (6H, m), 7.25-7.17 (3H, m), 7.08-7.05 (2H, m), 5.23 (1H, d, *J* = 6.0 Hz), 5.08 (1H, d, *J* = 15 Hz), 4.74-4.62 (1H, m), 4.14 (1H, d, *J* = 7.2 Hz), 3.97 (1H, d, *J* = 13 Hz), 2.82 (1H, dd, *J* = 0.6, 3.0 Hz), 2.69 (1H, dd, *J* = 6.9, 13 Hz), 1.87 (3H, s), 1.80 (3H, s), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 138.4, 137.4, 135.6, 135.6, 133.5, 129.7, 129.6, 128.2, 127.8, 127.7, 126.3, 125.1, 62.5, 48.2, 41.4, 26.8, 23.4, 21.1, 19.3. HRMS (ESI): Exact mass calcd for $C_{30}H_{38}NO_2Si$ *ie* $[M+H]^+$ 472.2672. Found 472.2723.

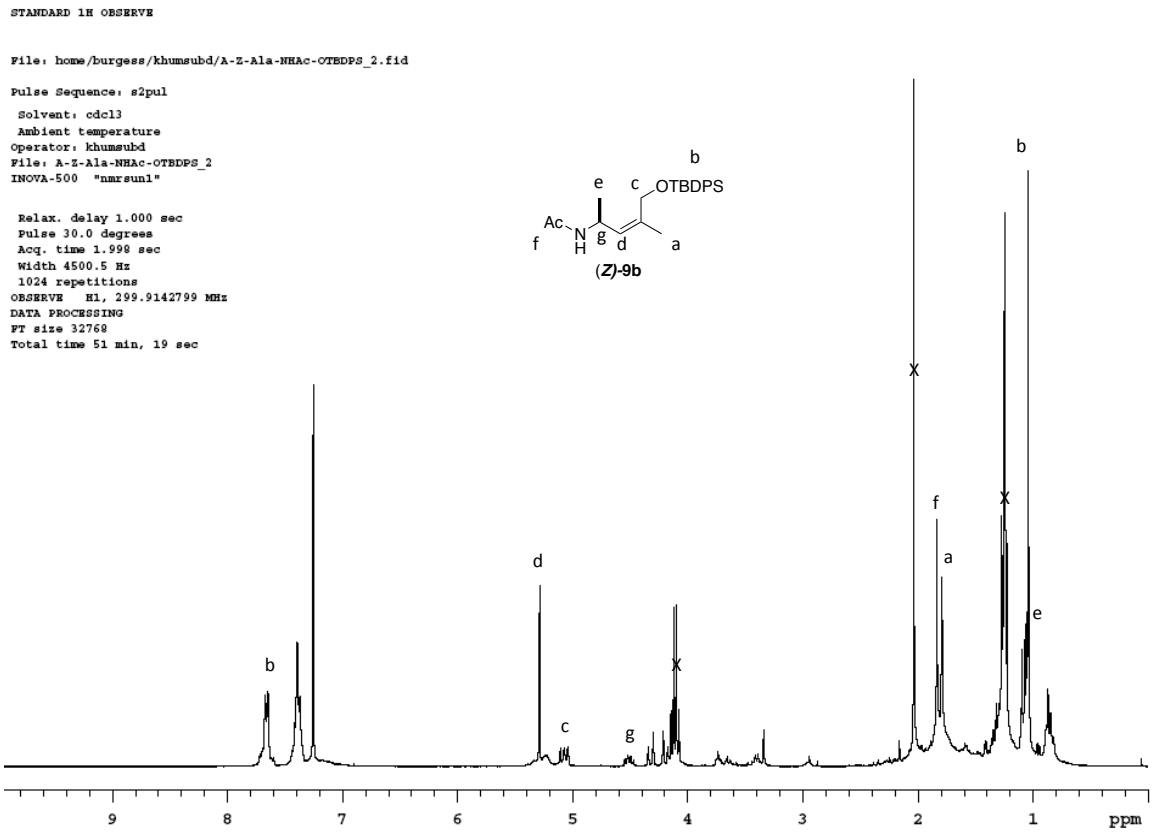

STANDARD 1H OBSERVE
File: home/burgess/yzhu/vnmrsys/data/III-ZY12-H.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: yzhu
File: III-ZY12-H
Mercury-300BB "mercury300"
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 299.9142799 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 50 sec
(Z)-9a
ppm

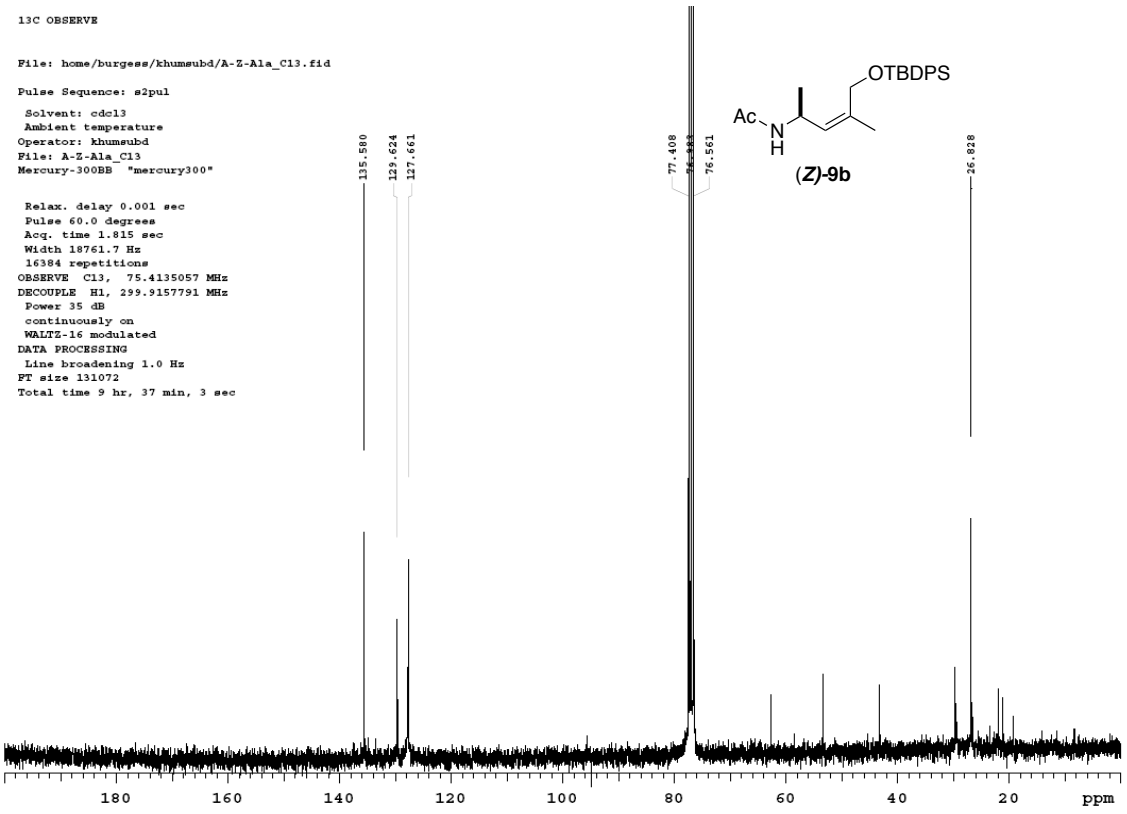

13C OBSERVE
File: home/burgess/yzhu/vnmrsys/data/III-ZY12-C13.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: yzhu
File: III-ZY12-C13
Mercury-300BB "mercury300"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
18000 repetitions
OBSERVE C13, 75.4135057 MHz
DECOUPLE H1, 299.9157791 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 10 hr, 33 min, 58 sec
(Z)-9a
ppm

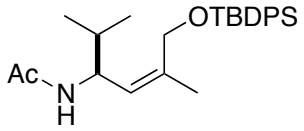


(***Z*)-9b**

(*S*)-*Z*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*Z*-9b). Product was obtained as a colorless oil (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.69 (4H, m), 7.46-7.41 (6H, m), 5.28-5.26 (1H, m), 5.12-5.09 (1H, m), 4.59-4.50 (1H, m), 4.30 (2H, dd, *J* = 12, 39 Hz), 1.88 (3H, s), 1.83 (3H, s), 1.08 (9H, s), 0.90 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 135.6, 135.5, 134.8, 133.9, 129.6, 127.7, 63.2, 53.9, 43.6, 29.2, 26.8, 22.5, 21.8. HRMS (ESI): Exact mass calcd for $C_{24}H_{34}NO_2Si$ *ie* $[M+H]^+$ 396.2359. Found 396.2570.

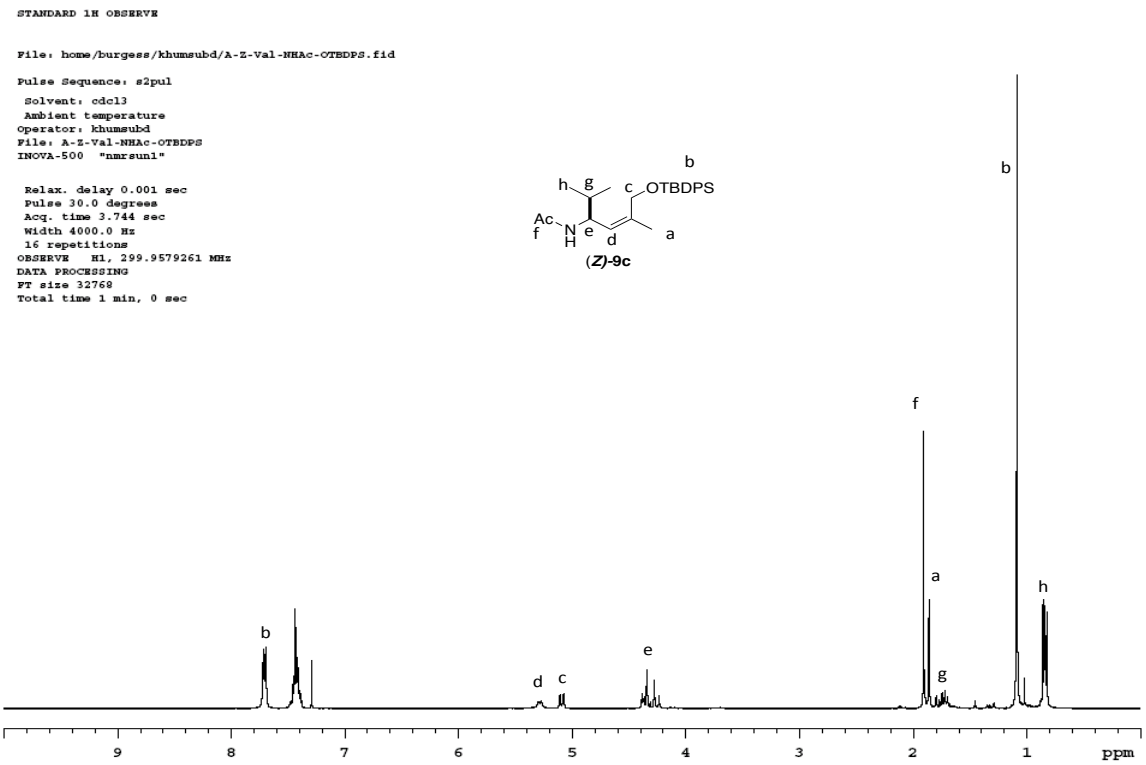


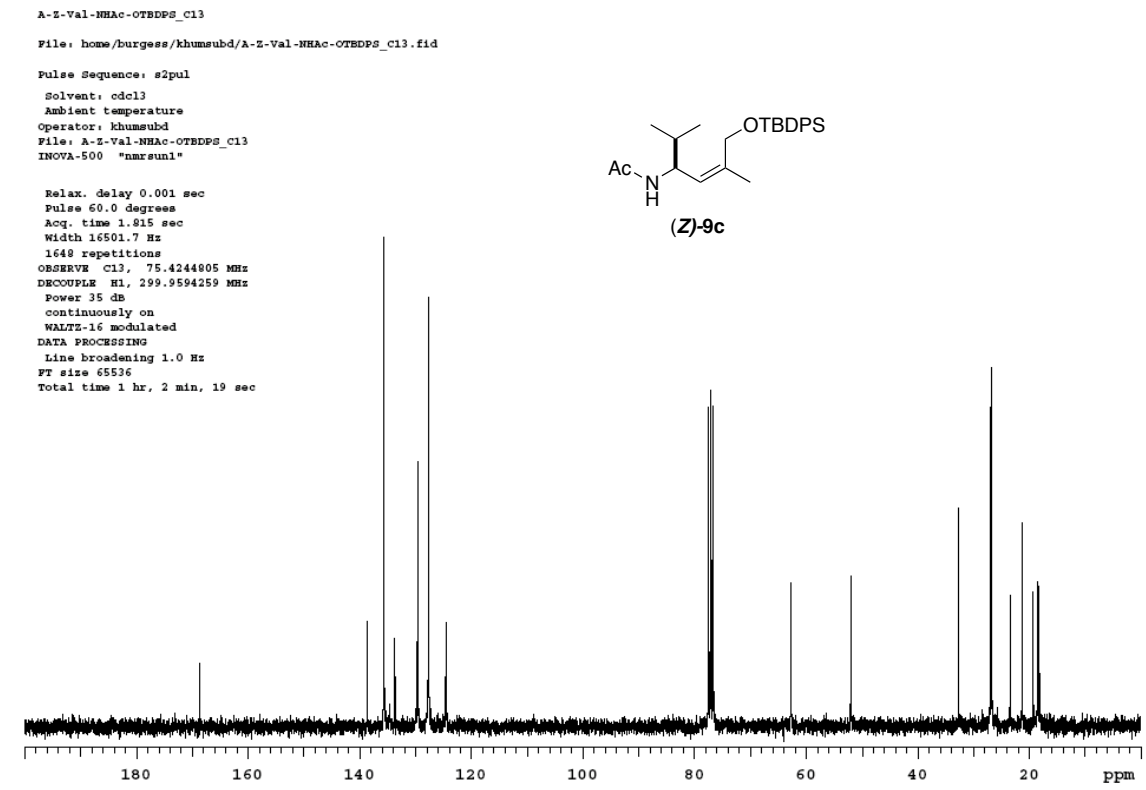


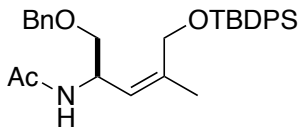


(*Z*)-9c

(*S*)-*Z*-*N*-(6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhex-4-en-3-yl)acetamide (*Z*-9c). Product was obtained as a colorless oil (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.69 (4H, m), 7.48-7.38 (6H, m), 5.28 (1H, d, *J* = 8.7 Hz), 5.09 (1H, dd, *J* = 1.2, 9.4 Hz), 4.39-4.36 (1H, m), 4.34 (1H, s), 4.28 (1H, d, *J* = 12 Hz), 1.91 (3H, s), 1.86 (3H, d, *J* = 1.2 Hz), 1.79-1.69 (1H, m), 1.09 (9H, s), 0.85 (3H, d, *J* = 3.9 Hz), 0.83 (3H, d, *J* = 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 138.7, 135.7, 133.7 (2 peaks), 129.6, 127.7, 124.6, 62.8, 52.0, 32.7, 26.9, 23.5, 21.4, 19.4, 18.6, 18.3. HRMS (ESI): Exact mass calcd for $C_{26}H_{38}NO_2Si$ *ie* $[M+H]^+$ 424.2672. Found 424.2689.

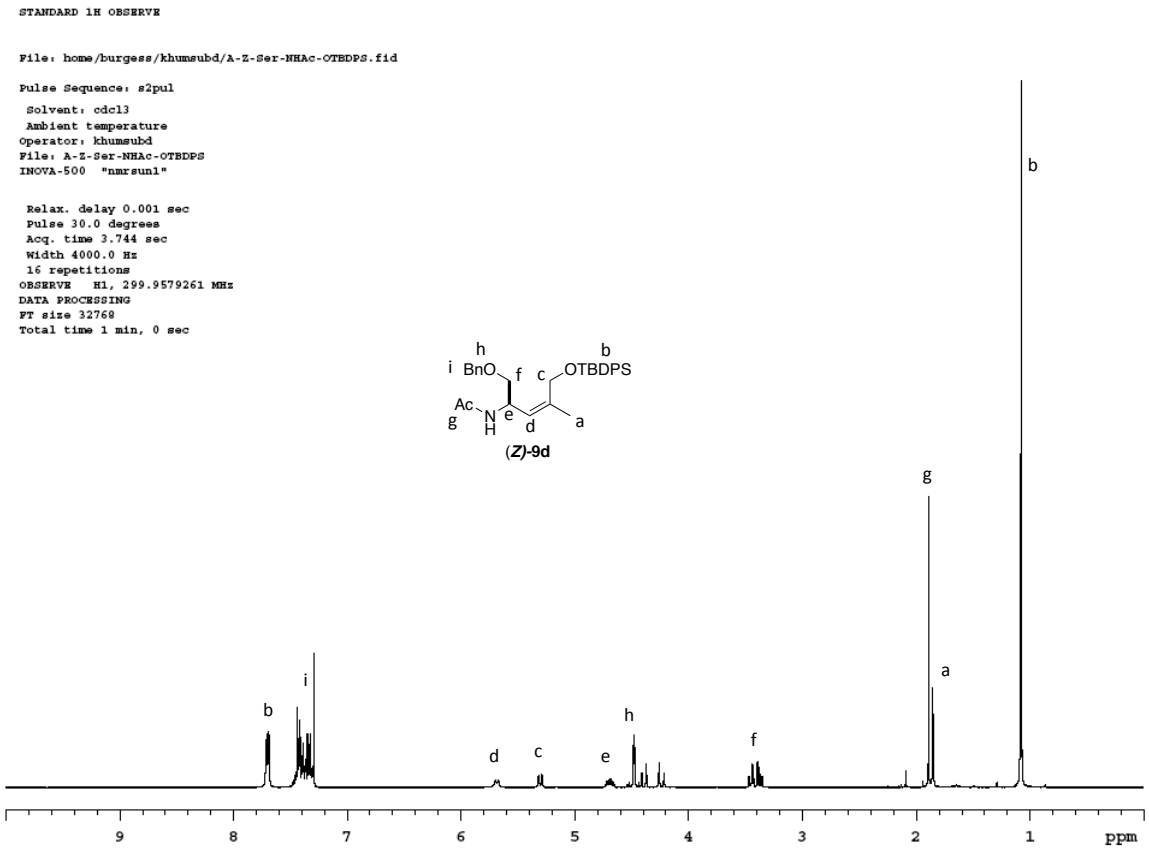

STANDARD 1H OBSERVE
File: home/burgess/khumsubd/A-Z-Val-NHAc-OTBDPS.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-Z-Val-NHAc-OTBDPS
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9579261 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
OTBDPS
Ac
N
H
(Z)-9c
ppm

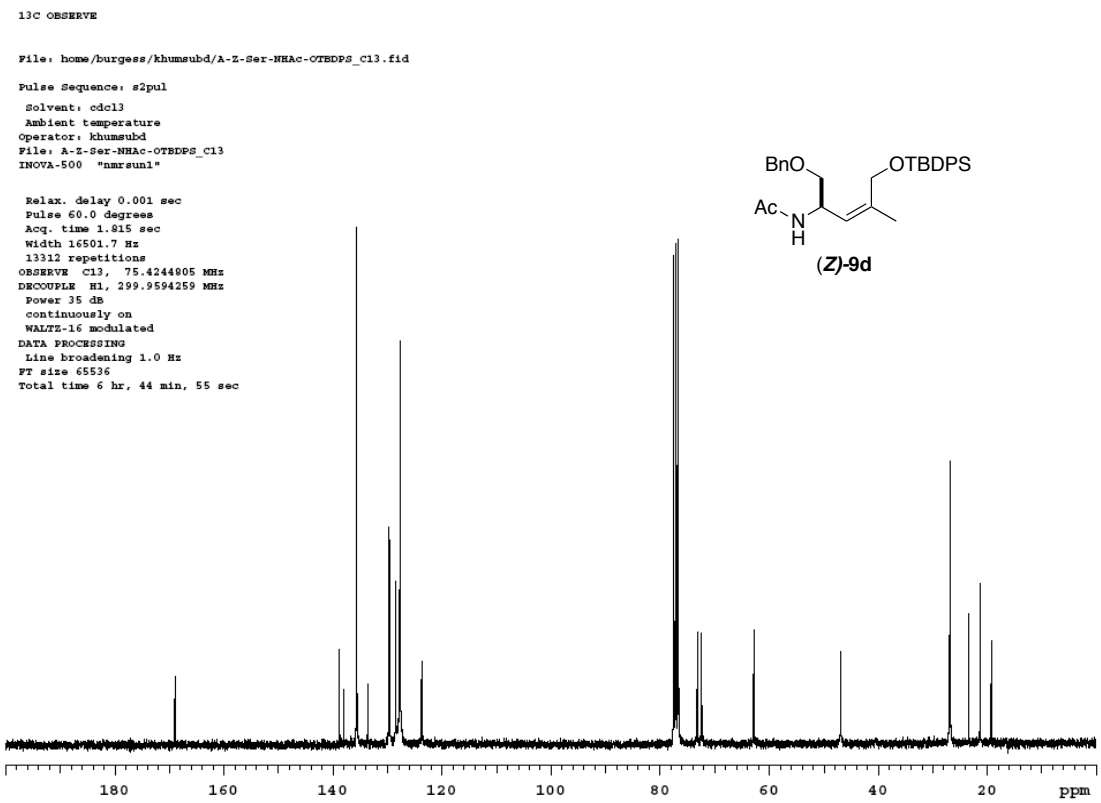

A-Z-Val-NHAc-OTBDPS_C13
File: home/burgess/khumsubd/A-Z-Val-NHAc-OTBDPS_C13.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-Z-Val-NHAc-OTBDPS_C13
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
1648 repetitions
OBSERVE C13, 75.4244905 MHz
DECOUPLE H1, 299.9594259 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 2 min, 19 sec
OTBDPS
Ac
N
H
(Z)-9c
ppm

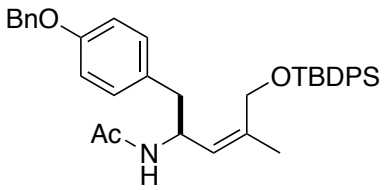


(*Z*)-**9d**

(*R*)-*Z*-*N*-(1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*Z*-9d). Product was obtained as a colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.68 (4H, m), 7.47-7.30 (11H, m), 5.69 (1H, d, *J* = 6.9 Hz), 5.30 (1H, dd, *J* = 1.5, 9 Hz), 4.71-4.66 (1H, m), 4.48 (2H, d, *J* = 2.1 Hz), 4.39 (1H, dd, *J* = 0.9, 12 Hz), 4.24 (1H, d, *J* = 13 Hz), 3.48-3.35 (2H, m), 1.89 (3H, s), 1.85 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 138.8, 138.0, 135.6, 133.6 (2 peaks), 129.7, 128.5, 127.8, 127.7, 123.8, 73.2, 72.4, 62.8, 46.9, 26.9, 23.4, 21.4, 19.3. HRMS (ESI): Exact mass calcd for $C_{31}H_{40}NO_3Si$ *ie* $[M+H]^+$ 502.2777. Found 502.2758.

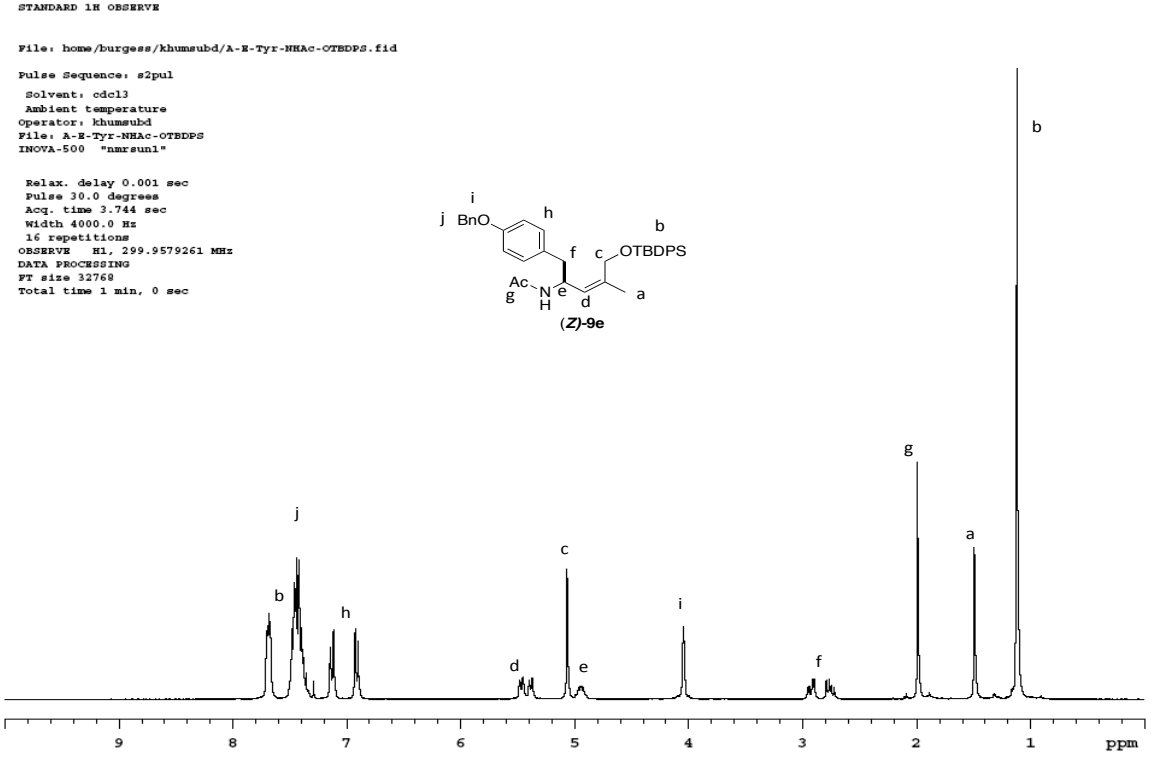


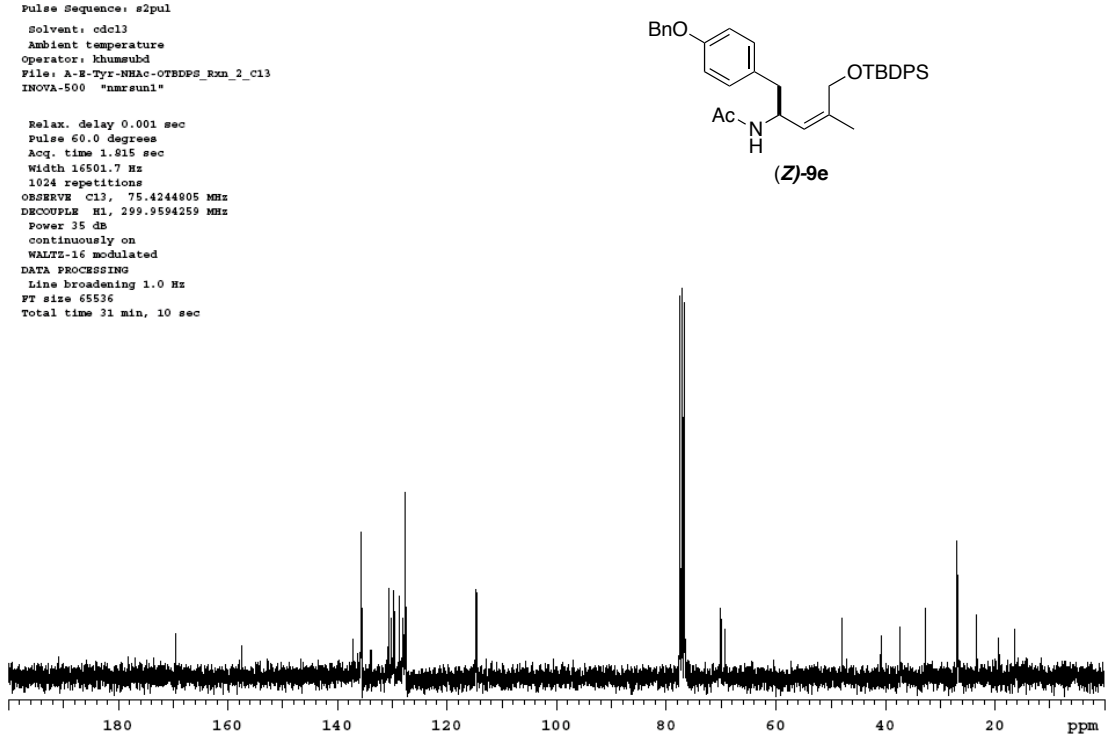




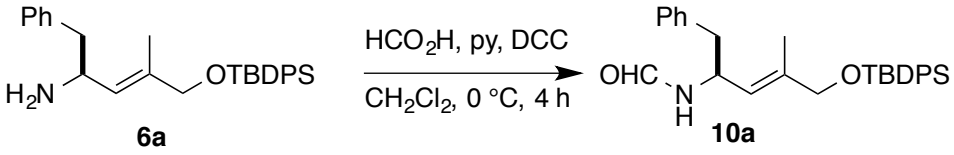
(*Z*)-**9e**

(*S*)-*Z*-*N*-(1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*Z*-9e). Product was obtained as a colorless oil (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.67 (4H, m), 7.48-7.40 (11H, m), 7.12 (2H, d, *J* = 13 Hz), 6.92 (2H, d, *J* = 8.0 Hz), 5.47 (1H, d, *J* = 0.9 Hz), 5.39 (1H, d, *J* = 6.0 Hz), 5.07 (2H, s), 5.01-4.89 (1H, m), 4.05 (2H, s), 2.92 (1H, dd, *J* = 3.0, 12 Hz), 2.85 (1H, dd, *J* = 0.9, 9.0 Hz), 2.00 (3H, s), 1.49 (3H, s), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 157.6, 138.1, 135.2 (2 peaks), 134.2, 134.0, 131.4, 129.7, 128.4, 127.4, 126.9, 126.3, 114.2, 70.1, 62.3, 48.7, 40.6, 26.2, 23.3, 20.9, 19.2. HRMS (ESI): Exact mass calcd for $C_{37}H_{44}NO_3Si$ *ie* $[M+H]^+$ 578.3090. Found 578.3077.


STANDARD 1H OBSERVE
File: home/burgess/khumsubd/A-E-Tyr-NHAc-OTBDPS.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-E-Tyr-NHAc-OTBDPS
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9579261 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
BnO
OTBDPS
Ac
N
H
(Z)-9e
ppm


13C OBSERVE
File: home/burgess/khumsubd/A-E-Tyr-NHAc-OTBDPS_Rxn_2_C13.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-E-Tyr-NHAc-OTBDPS_Rxn_2_C13
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
1024 repetitions
OBSERVE C13, 75.4244905 MHz
DECOUPLE H1, 299.9594259 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 31 min, 10 sec
BnO
OTBDPS
Ac
N
H
(Z)-9e
ppm

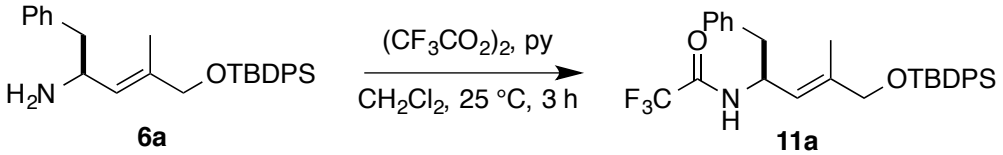
Synthesis Of (*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)formamide (10a).



6a **10a**

Formic acid (0.2 g, 5 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a solution of DCC (0.5 g, 2.5 mmol) in 3 mL CH_2Cl_2 at 0 ^oC. The mixture was stirred for 5 min then added to an ice-bath cooled solution of *O*-TBDPS-allylic amine **8a** (0.4 g, 1 mmol) in 3 mL pyridine. The mixture was then stirred in ice-bath for 4 h. The solid was removed via filtration, and washed with Et_2O (10 mL). The combined extracts were evaporated and purified by flash chromatography using 40% EtOAc/hexanes giving formamide **10a** as a colorless oil (0.4 g, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.63 (4H, m), 7.48-7.31 (6H, m), 7.29-7.19 (5H, m), 5.45 (1H, dd, *J* = 1.2, 9.1 Hz), 5.31 (1H, d, *J* = 6.0 Hz), 5.10-5.00 (1H, m), 4.02 (1H, s), 2.98 (1H, dd, *J* = 5.4, 13 Hz), 2.82 (1H, dd, *J* = 7.5, 13 Hz), 1.59 (2H, s), 1.47 (3H, d , *J* = 0.6 Hz), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 160.0, 138.4, 138.0, 137.2, 136.5, 135.5 (2 peaks), 133.6, 133.5, 129.8, 129.7 (2 peaks), 126.9, 126.5, 122.3, 121.7, 67.5 (2 peaks), 61.3, 46.8, 43.4, 41.5, 26.8, 19.3, 13.8 (2 peaks). HRMS (ESI): Exact mass calcd for $C_{29}H_{36}NO_2Si$ *ie* $[M+H]^+$ 458.2515. Found 458.2577.

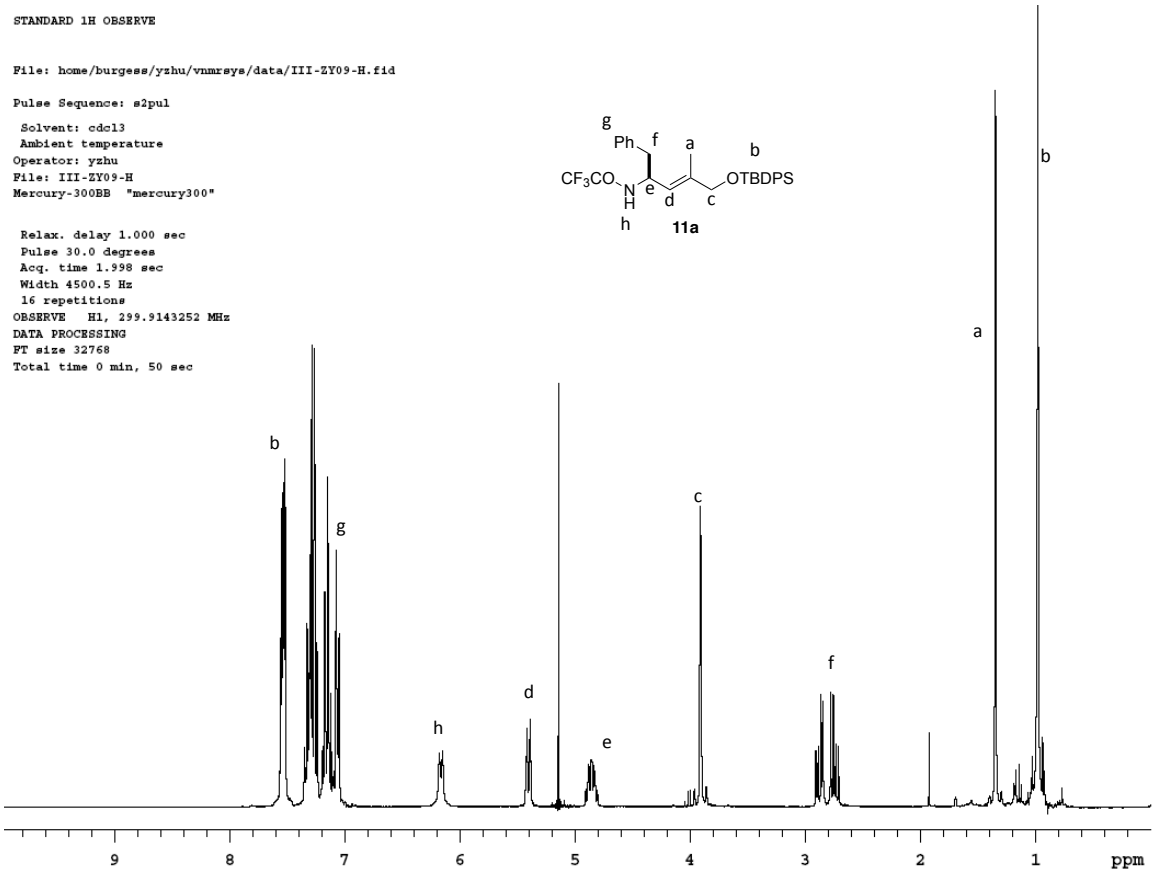
Synthesis Of (*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)-2,2,2-trifluoroacetamide (11a).

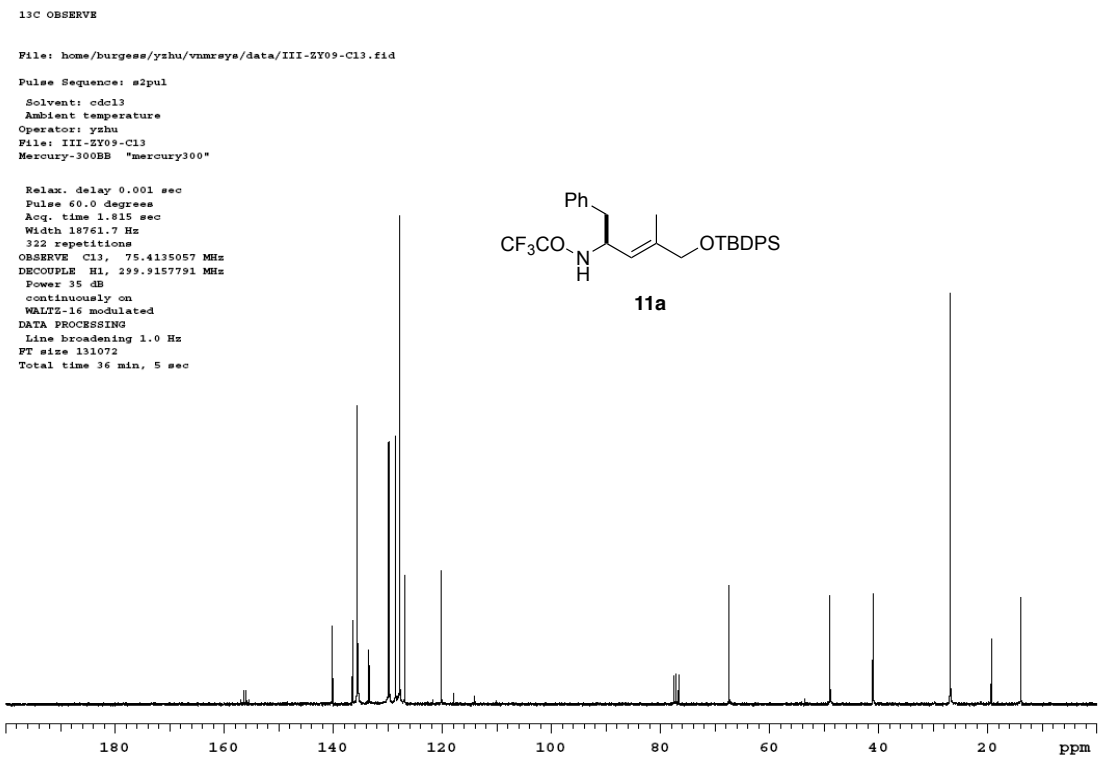


6a **11a**

O-TBDPS-allylic amine **8a** (0.2 g, 0.5 mmol) was dissolved in 2 mL CH_2Cl_2 and cooled to 0 ^oC. Trifluoroacetic anhydride (76 μL, 0.6 mmol) was added dropwise to this solution followed by pyridine (61 μL, 0.8 mmol). The mixture was stirred for 2 h at 25 ^oC, then another aliquot of trifluoroacetic anhydride (38 μL, 0.3 mmol) and pyridine (30

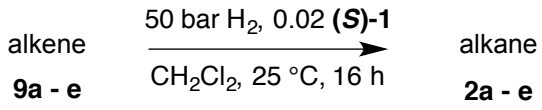
μL, 0.4 mmol) were added to this solution and stirred for an additional 1 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using 10% EtOAc/hexanes giving acetamide **11a** as a colorless oil (0.3 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.65 (4H, m), 7.49-7.37 (6H, m), 7.34-7.18 (5H, m), 6.30 (1H, d, *J* = 8.0 Hz), 5.56-5.52 (1H, m), 5.02-4.97 (1H, m), 4.05 (2H, s), 3.01 (1H, dd, *J* = 5.4, 13 Hz), 2.88 (1H, dd, *J* = 7.8, 13 Hz), 1.48 (3H, d, *J* = 1.2 Hz), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 155.9, 140.1, 136.4, 135.5 (2 peaks), 133.5, 133.4, 129.8, 129.7, 128.6, 128.1, 127.8, 126.8, 120.2, 117.8, 114.0, 67.4, 48.9, 41.0, 26.9, 19.3, 13.9. HRMS (ESI): Exact mass calcd for $C_{30}H_{34}F_3LiNO_2Si$ *ie* $[M+H]^+$ 532.2471. Found 532.2474.

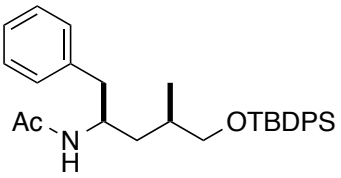




B. General Procedure for Catalytic Hydrogenation.

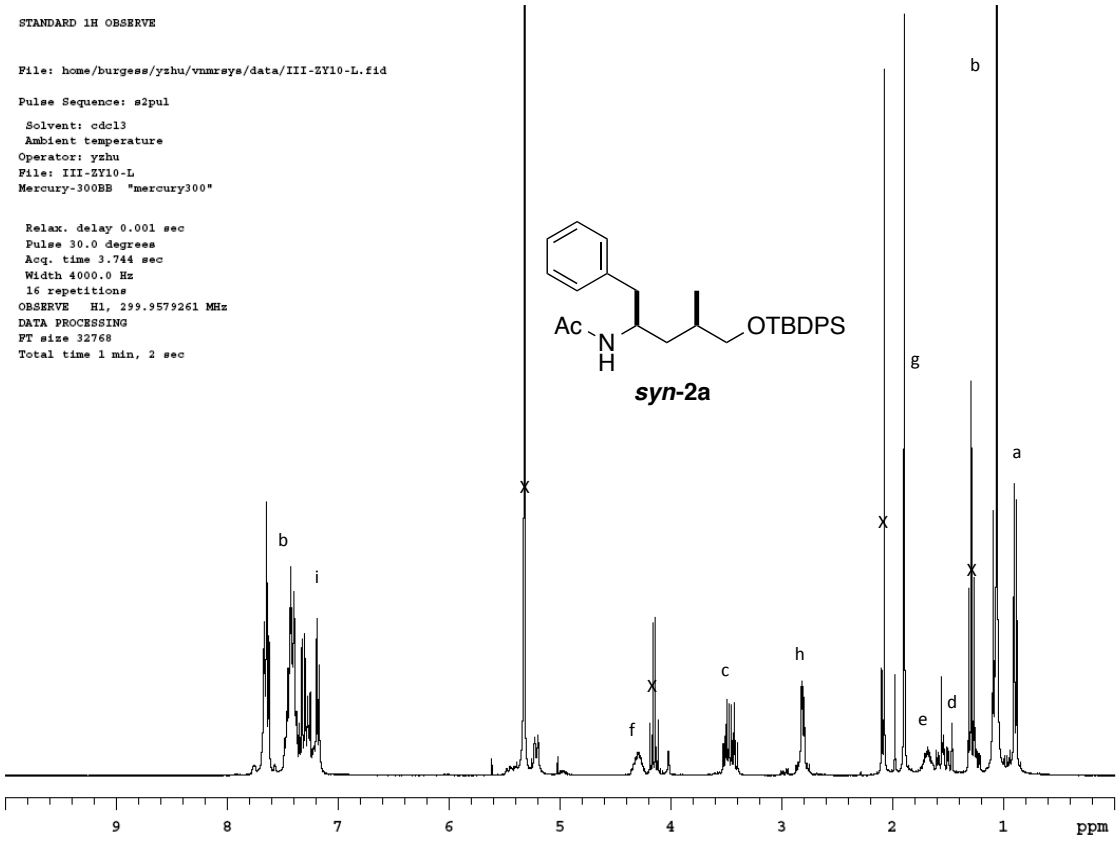
The corresponding alkenes (0.1 mmol) and **(*S*)-1** (2 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 50% EtOAc/hexanes as the eluent. The diastereomeric ratio was then measured through HPLC analysis using unbonded silica 300 Å column.

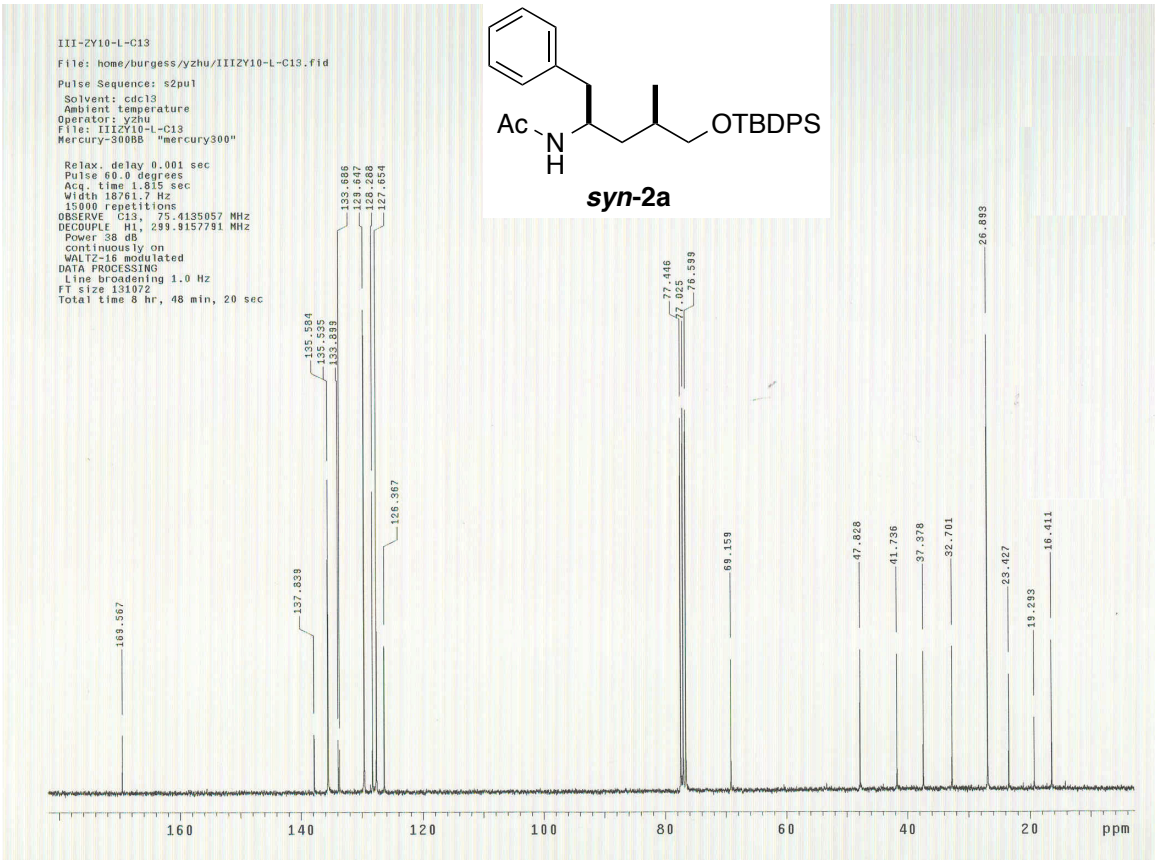


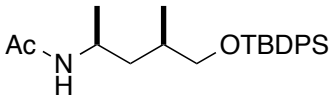


***syn*-2a**

***N*-((2*R*,4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpentan-2-yl)acetamide (*syn*-2a).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.62 (4H, m), 7.46-7.35 (6H, m), 7.33-7.17 (5H, m), 5.17 (1H, d, *J* = 9.0 Hz), 4.39-4.21 (1H, m), 3.52-3.40 (2H, m), 2.83-2.80 (2H, m), 1.89 (3H, s), 1.78-1.64 (1H, m), 1.55 (1H, s), 1.30-1.21 (1H, s), 1.07 (9H, s), 0.89 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 137.8, 135.6, 135.5, 133.9, 133.7, 129.6, 128.3, 127.8, 126.4, 69.2, 47.8, 41.4, 37.4, 32.7, 26.9, 23.4, 19.3, 16.4. HRMS (ESI): Exact mass calcd for $C_{30}H_{40}NO_2Si$ *ie* $[M+H]^+$ 474.2828. Found 474.2832.

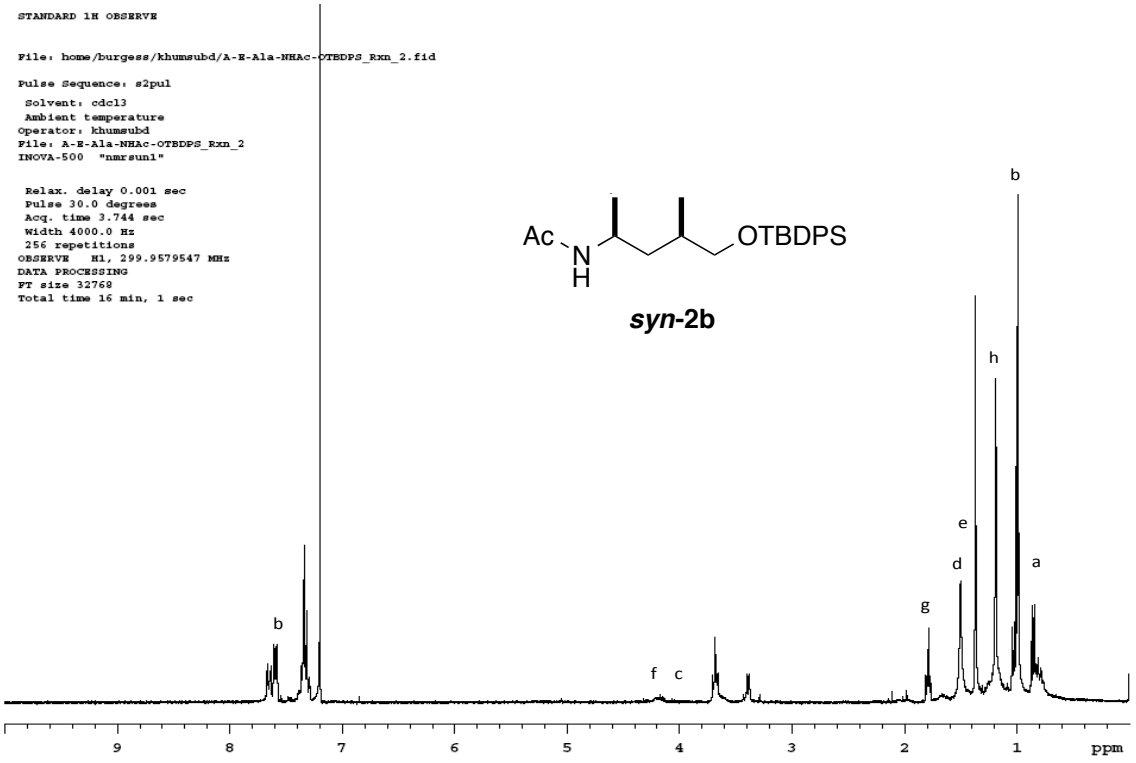


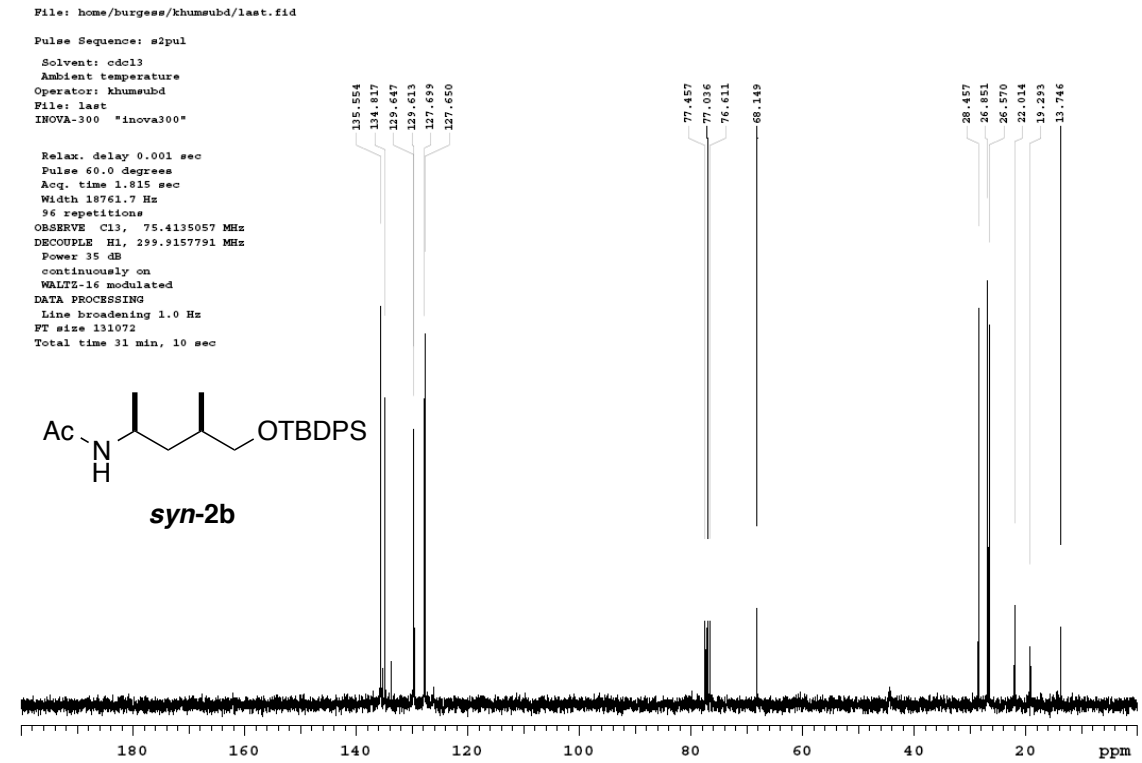


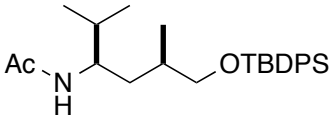


***syn*-2b**

***N*-(2*S*,4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*syn*-2b).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (4H, m), 7.43-7.36 (6H, m), 5.12 (1H, d, *J* = 8.7 Hz), 4.13-3.97 (1H, m), 4.06-4.01 (1H, m), 1.88 (3H, s), 1.79-1.60 (1H, m), 1.62 (1H, s), 1.25-1.13 (2H, m), 1.11 (3H, d, *J* = 3.3 Hz), 1.08 (9H, s), 0.91 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.8, 129.6 (2 peaks), 127.7 (2 peaks), 68.1, 28.5, 26.9, 26.6, 22.0, 19.3, 13.7. HRMS (ESI): Exact mass calcd for $C_{24}H_{36}NO_2Si$ *ie* $[M+H]^+$ 398.2515 Found 398.2552.

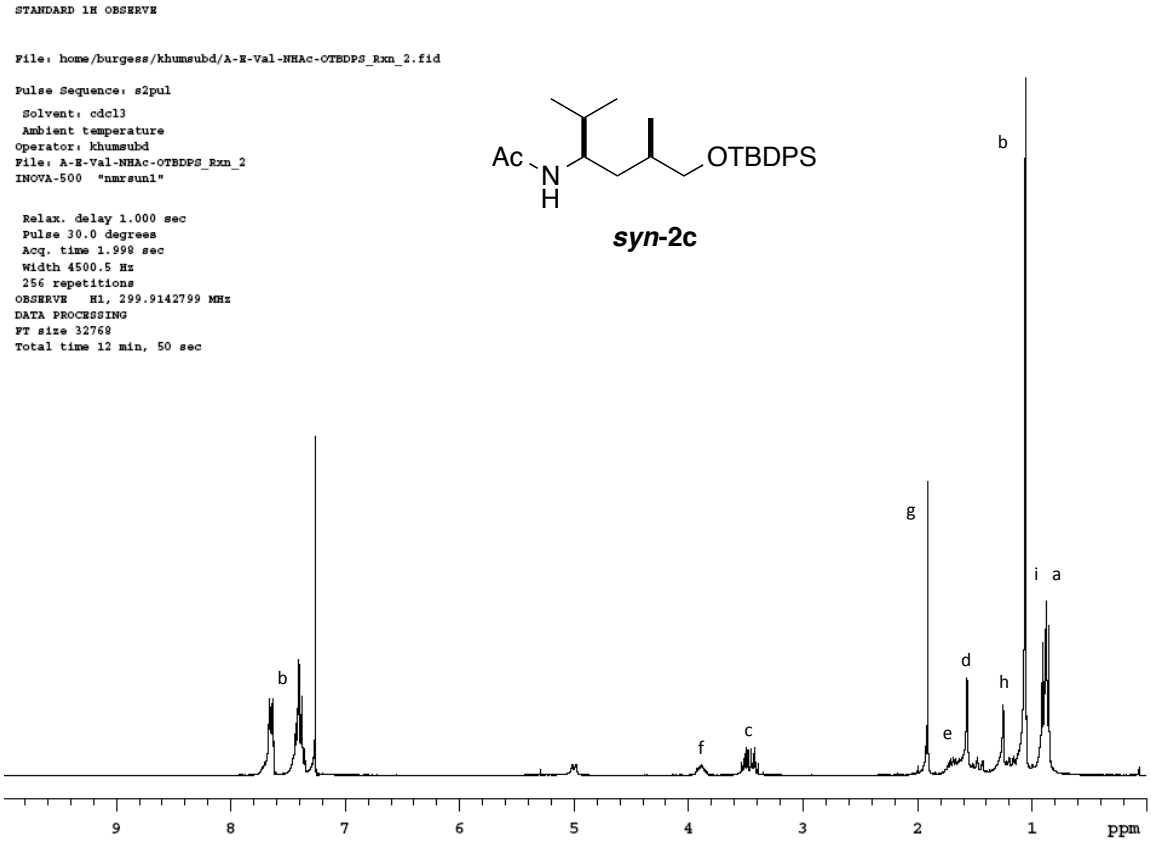

STANDARD 1H OBSERVE
File: home/burgess/khumsubd/A-E-Ala-NHAc-OTBDPS_Rxn_2.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-E-Ala-NHAc-OTBDPS_Rxn_2
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
256 repetitions
OBSERVE H1, 299.9579547 MHz
DATA PROCESSING
FT size 32768
Total time 16 min, 1 sec
Ac
N
H
OTBDPS
syn-2b
b
f
c
g
d
e
h
a
9
8
7
6
5
4
3
2
1
ppm

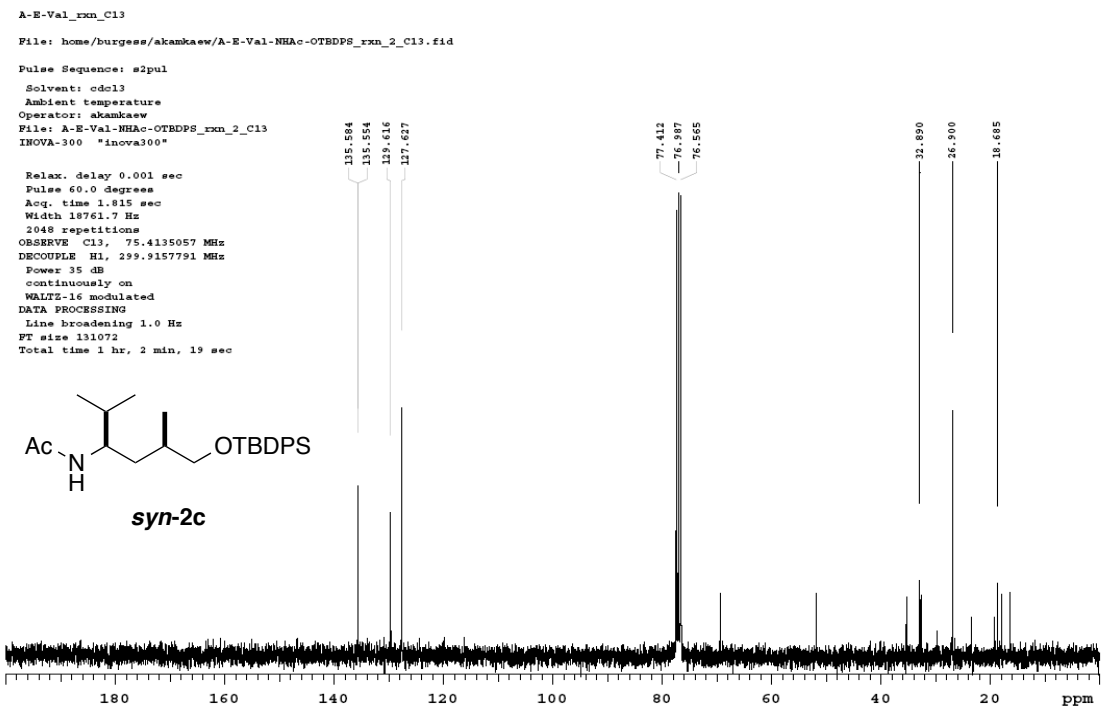

File: home/burgess/khumsubd/last.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: last
INOVA-300 "inova300"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
96 repetitions
OBSERVE C13, 75.4135057 MHz
DECOUPLE H1, 299.9157791 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 31 min, 10 sec
135.554
134.817
129.647
129.613
127.699
127.650
77.457
77.036
76.611
68.149
28.457
26.851
26.570
22.014
19.293
13.746
Ac
N
H
OTBDPS
syn-2b
180
160
140
120
100
80
60
40
20
ppm



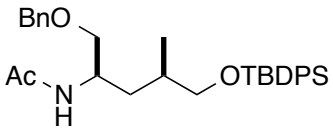
***syn*-2c**

***N*-((3*R*,5*R*)-6-((tert-Butyldiphenylsilyl)oxy)-2,5-dimethylhexan-3-yl)acetamide (*syn*-2c)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (4H, m), 7.41-7.38 (6H, m), 5.00 (1H, d, *J* = 9.9 Hz), 3.91-3.88 (1H, m), 3.53-3.39 (2H, m), 1.91 (3H, s), 1.78-1.55 (1H, m), 1.56 (1H, s), 1.52-1.45 (1H, m), 1.19-1.10 (1H, m), 1.06 (9H, s), 0.91-0.84 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (2 peaks), 129.6, 127.6 (2 peaks), 69.8, 51.9, 37.4, 33.1, 33.0, 26.9, 23.7, 19.8, 19.3, 19.1, 16.2. HRMS (ESI): Exact mass calcd for $C_{26}H_{40}NO_2Si$ *ie* $[M+H]^+$ 426.2828. Found 426.2851.



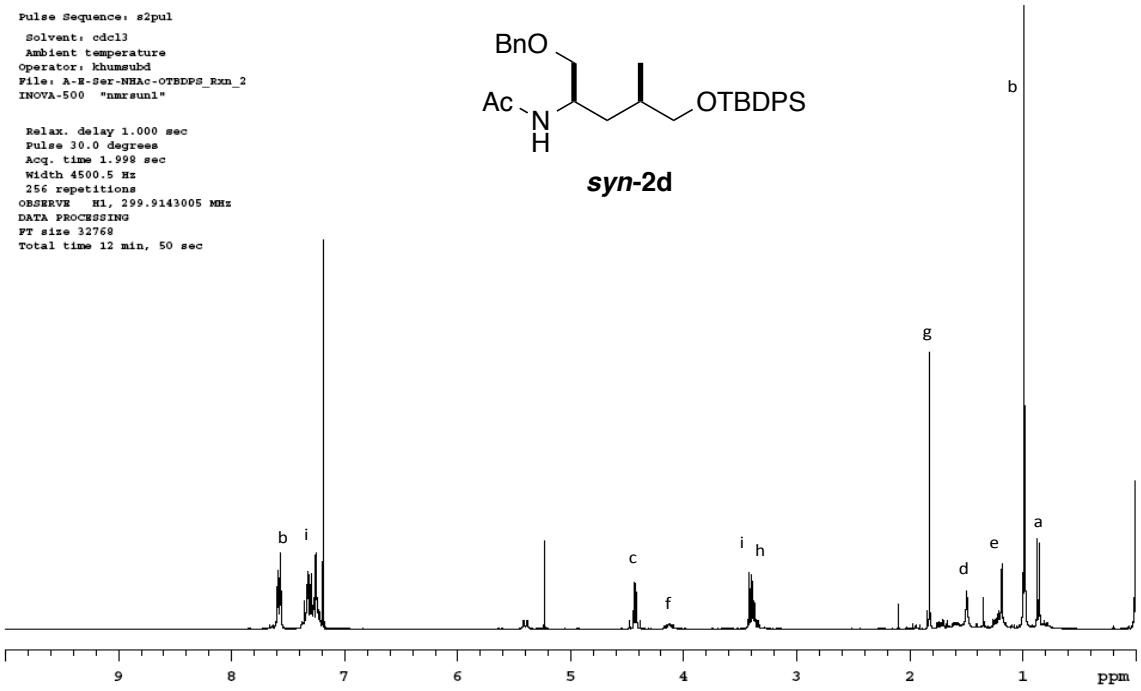


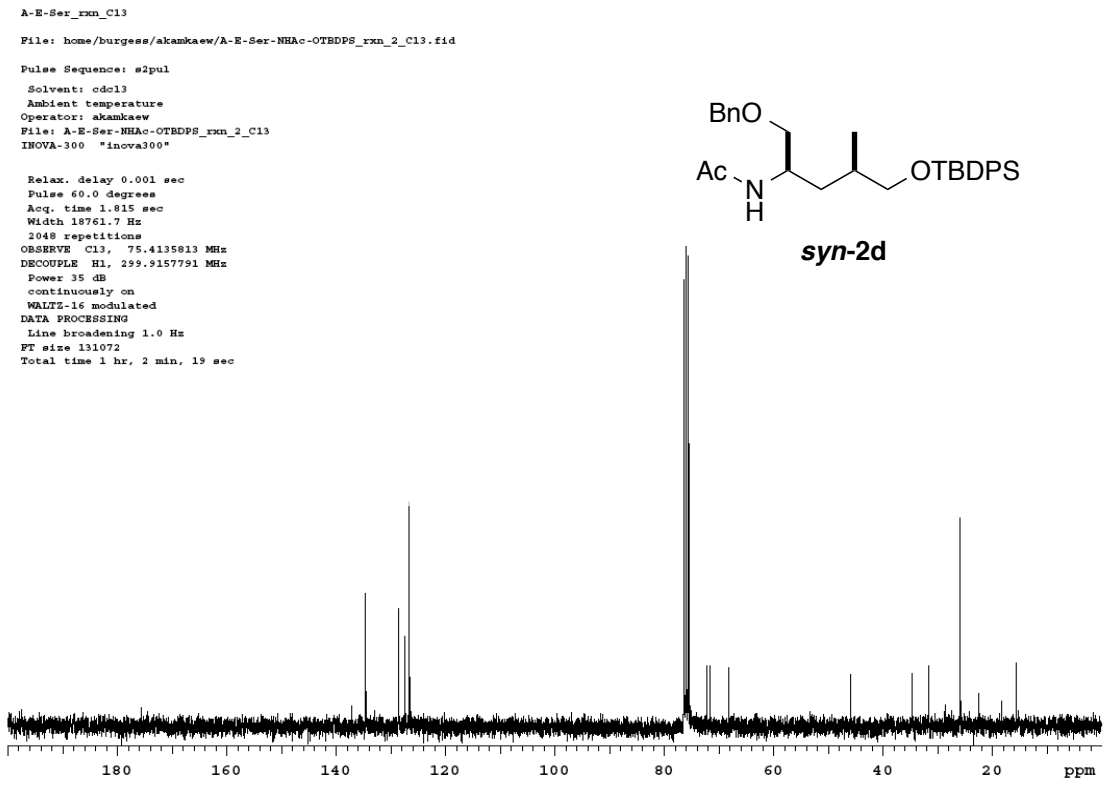
***syn*-2c**

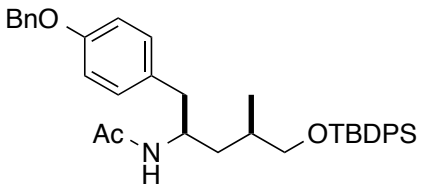


***syn*-2d**

***N*-((2*R*,4*R*)-1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*syn*-2d).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (4H, m), 7.40-7.32 (11H, m), 5.47 (1H, d, *J* = 9.0 Hz), 4.50 (2H, dd, *J* = 12, 17 Hz), 4.24-4.12 (1H, m), 3.50-3.43 (4H, m), 1.89 (3H, s), 1.80-1.76 (1H, m), 1.73-1.59 (1H, m), 1.27-1.20 (1H, m), 1.16 (9H, s), 0.93 (3H, d, *J* = 6.6Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 129.6, 128.4, 127.6 (2 peaks), 73.5, 72.8, 69.9, 47.0, 36.1, 33.2, 27.0, 23.8, 19.2, 18.0. HRMS (ESI): Exact mass calcd for $C_{31}H_{42}NO_3Si$ *ie* $[M+H]^+$ 504.2934. Found 504.2952.

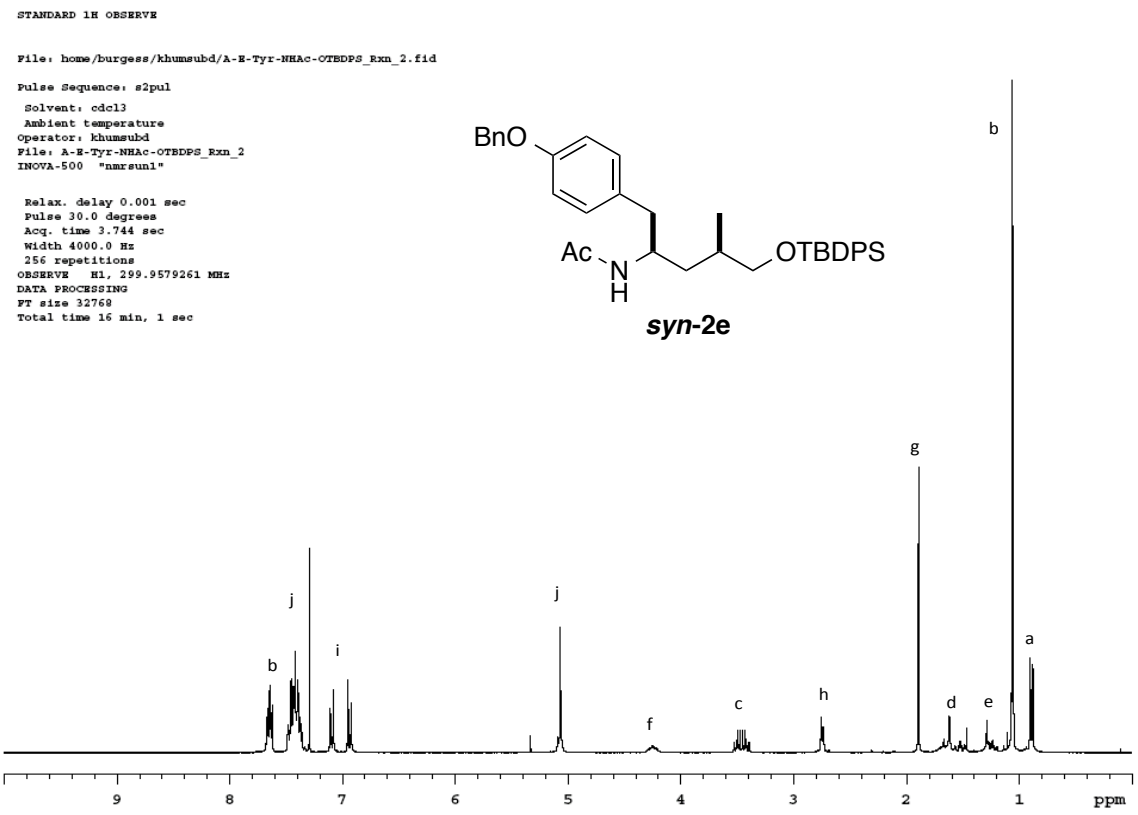

STANDARD 1H OBSERVE
File: home/burgess/khumsubd/A-E-Ser-NHAc-OTBDPS_Rxn_2.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-E-Ser-NHAc-OTBDPS_Rxn_2
INOVA-500 "nmrsun1"
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
256 repetitions
OBSERVE H1, 299.9143005 MHz
DATA PROCESSING
FT size 32768
Total time 12 min, 50 sec
BnO
Ac
N
H
OTBDPS
syn-2d
b
i
c
f
i
h
g
d
e
b
a
9
8
7
6
5
4
3
2
1
ppm

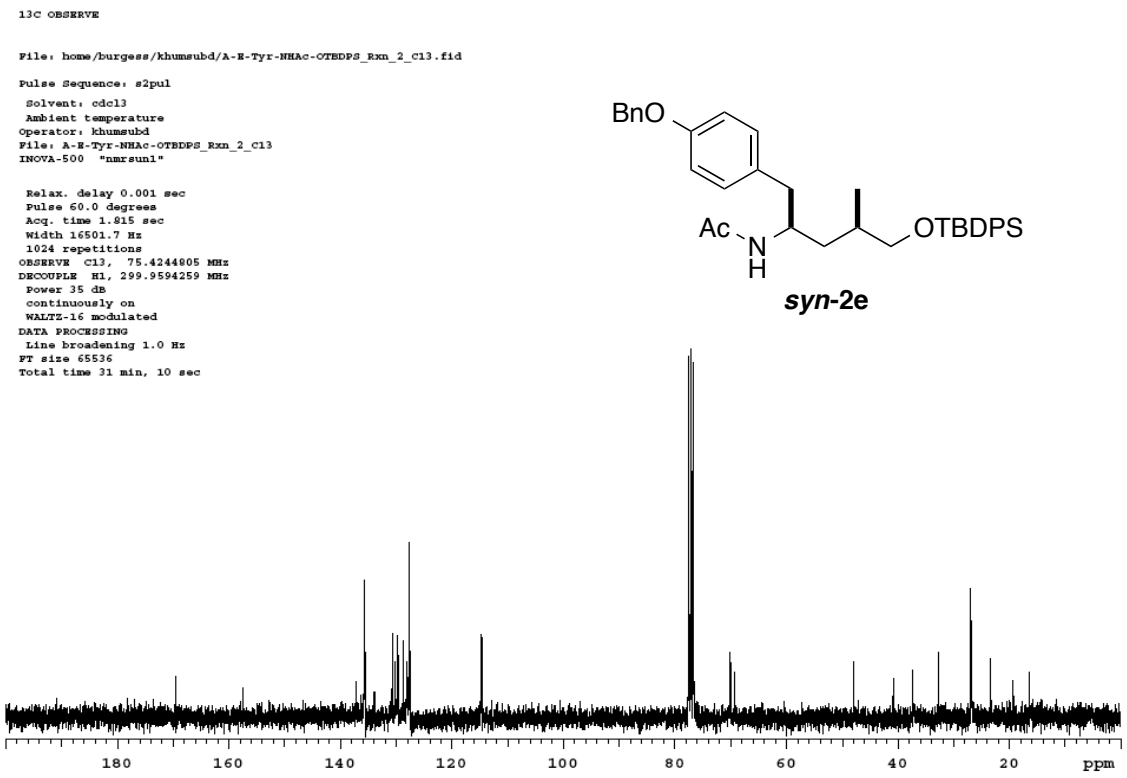

A-E-Ser_rxn_C13
File: home/burgess/akamkaew/A-E-Ser-NHAc-OTBDPS_rxn_2_C13.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: akamkaew
File: A-E-Ser-NHAc-OTBDPS_rxn_2_C13
INOVA-300 "inova300"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
2048 repetitions
OBSERVE C13, 75.4135813 MHz
DECOUPLE H1, 299.9157791 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 2 min, 19 sec
BnO
Ac
N
H
OTBDPS
syn-2d
180
160
140
120
100
80
60
40
20
ppm



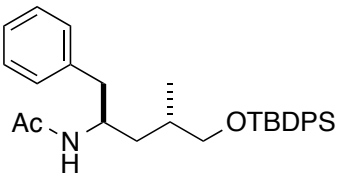
***syn*-2e**

***N*-((2*R*,4*R*)-1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*syn*-2e).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.62 (4H, m), 7.45-7.37 (11H, m), 7.09 (2H, d, *J* = 8.4 Hz), 6.94 (2H, d, *J* = 8.4 Hz), 5.07 (2H, s), 4.32-4.19 (1H, m), 3.53-3.40 (2H, m), 2.76 (1H, s), 2.74 (1H, d, *J* = 2.1 Hz), 1.89 (3H, s), 1.78-1.60 (1H, m), 1.62 (1H, s), 1.59-1.46 (1H, m), 1.30-1.19 (1H, m), 1.06 (9H, s), 0.89 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 157.5, 137.1, 135.6 (2 peaks), 130.6, 130.2, 129.7, 128.6, 128.0, 127.7, 127.5, 114.7, 70.0, 69.2, 47.9, 40.0, 37.4, 32.7, 26.9, 23.5, 19.3, 16.5. HRMS (ESI): Exact mass calcd for $C_{37}H_{46}NO_3Si$ *ie* $[M+H]^+$ 580.3247. Found 580.3253.



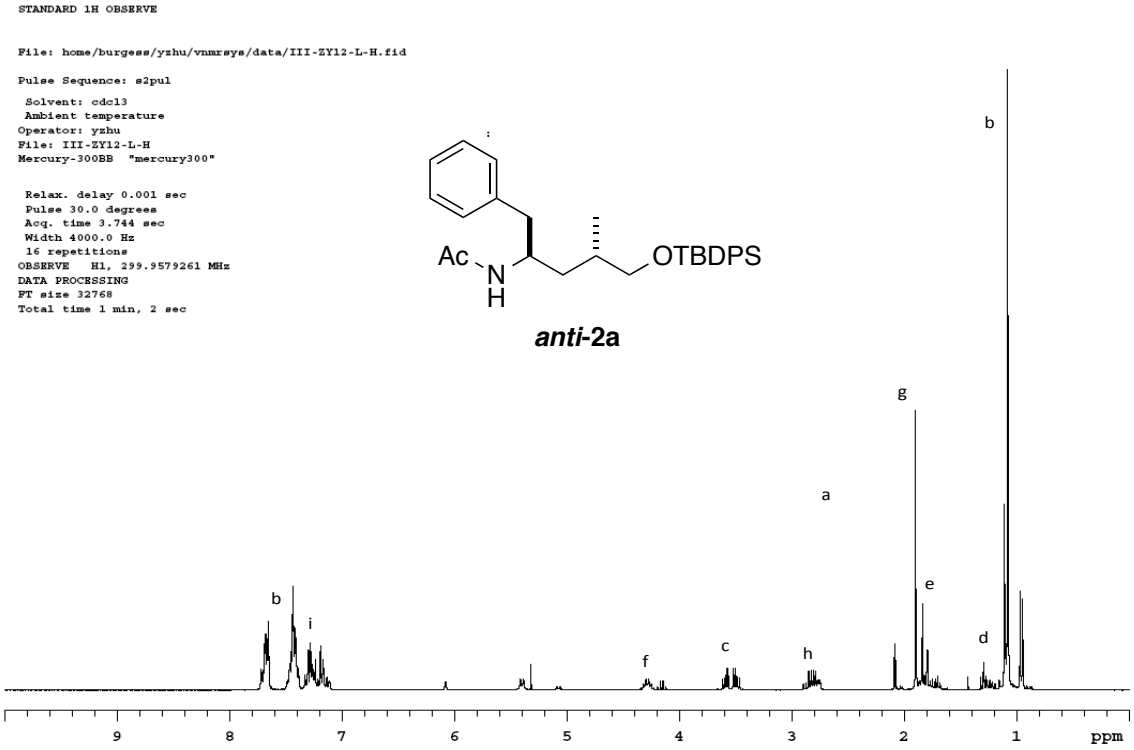


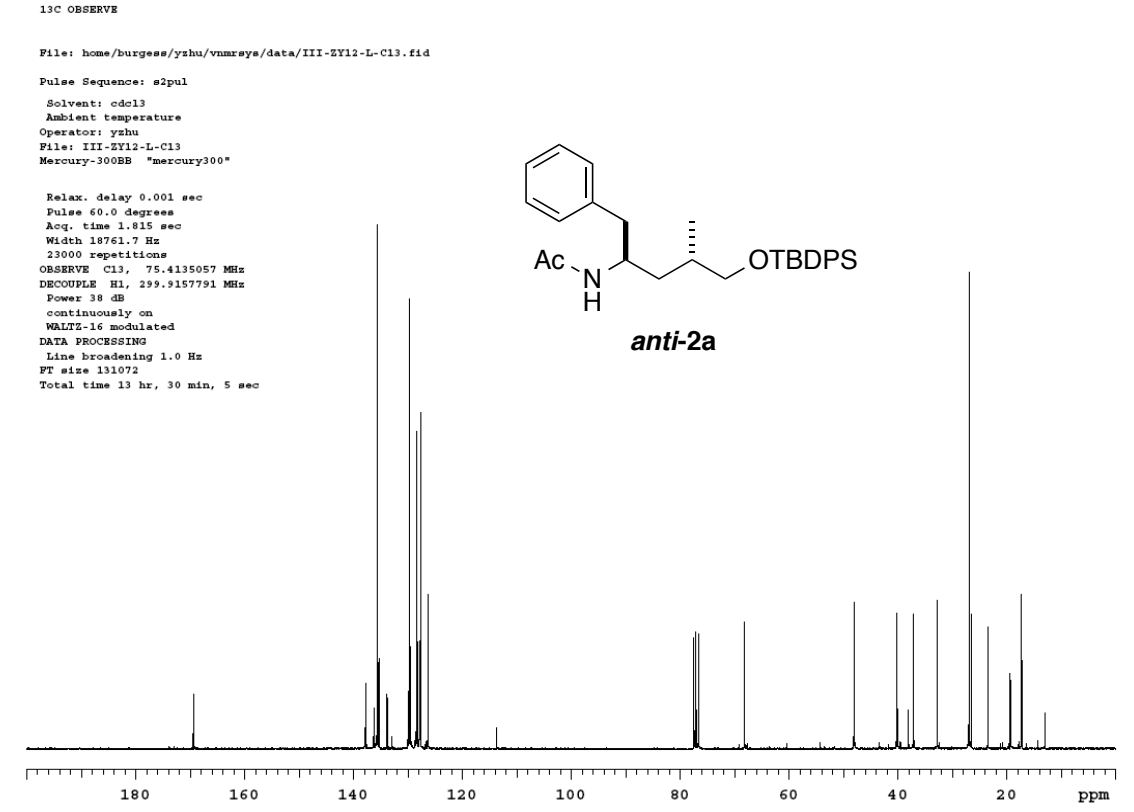
***syn*-2e**

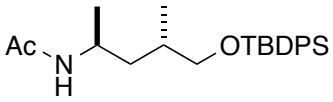


***anti*-2a**

***N*-((2*R*,4*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpentan-2-yl)acetamide (*anti*-2a)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.65 (4H, m), 7.48-7.38 (6H, m), 7.33-7.11 (5H, m), 5.40 (1H, d, *J* = 8.7 Hz), 4.38-4.22 (1H, m), 3.59 (1H, dd, *J* = 5.4, 10 Hz), 3.49 (1H, dd, *J* = 5.6, 10 Hz), 2.85-2.75 (2H, m), 1.90 (3H, s), 1.88-1.70 (2H, m), 1.29-1.24 (1H, m), 1.08 (9H, s), 0.96 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 137.9, 137.8, 136.3, 135.6, 135.4, 135.3, 133.8, 133.7, 130.0 (2 peaks), 129.6, 129.5, 128.3 (2 peaks), 127.9, 127.8, 127.7, 127.6, 126.4, 126.3, 113.7, 68.2, 48.0 (2 peaks), 40.2, 41.0, 38.0, 37.1, 32.8, 26.9, 26.5, 23.5, 23.4, 19.3, 19.2, 17.2, 12.9. HRMS (ESI): Exact mass calcd for $C_{30}H_{40}NO_2Si$ *ie* $[M+H]^+$ 474.2828. Found 474.2833.

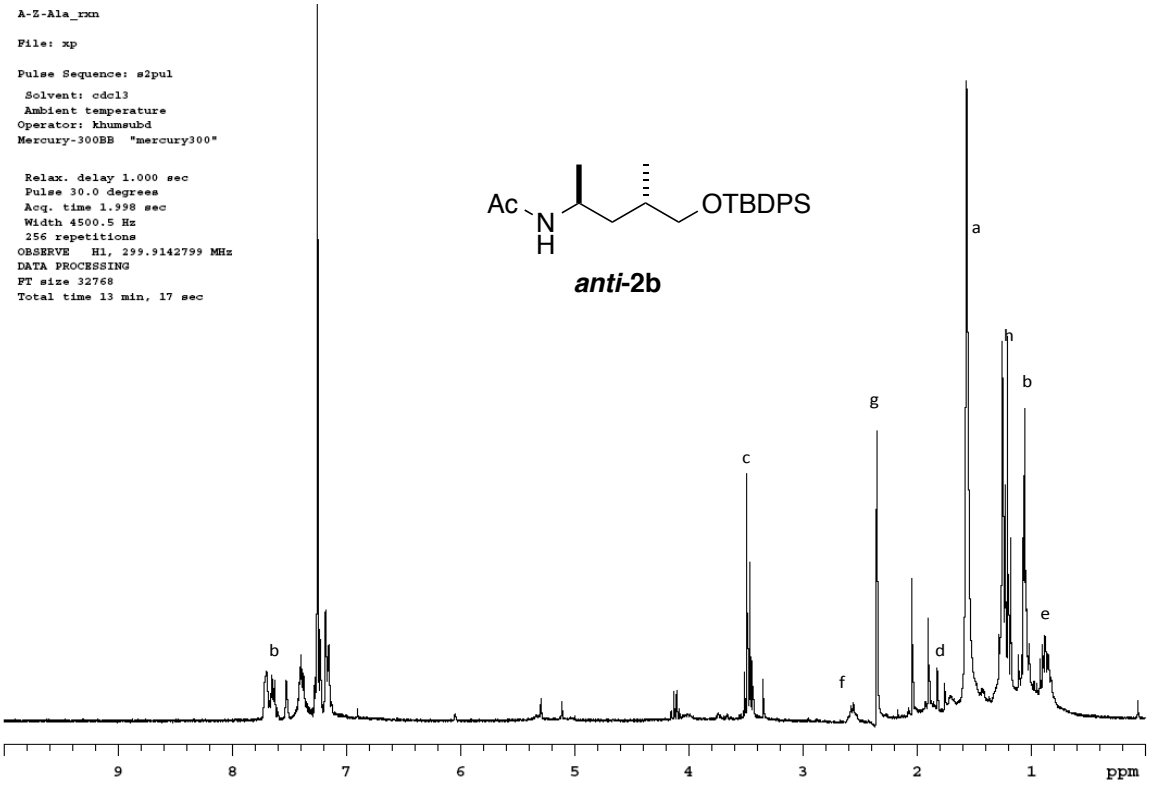

STANDARD 1H OBSERVE
File: home/burgess/yzhu/vnmrsys/data/III-ZY12-L-H.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: yzhu
File: III-ZY12-L-H
Mercury-300BB "mercury300"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9579261 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 2 sec
Ac
N
H
OTBDPS
anti-2a
b
g
a
e
d
c
h
f
i
9
8
7
6
5
4
3
2
1
ppm

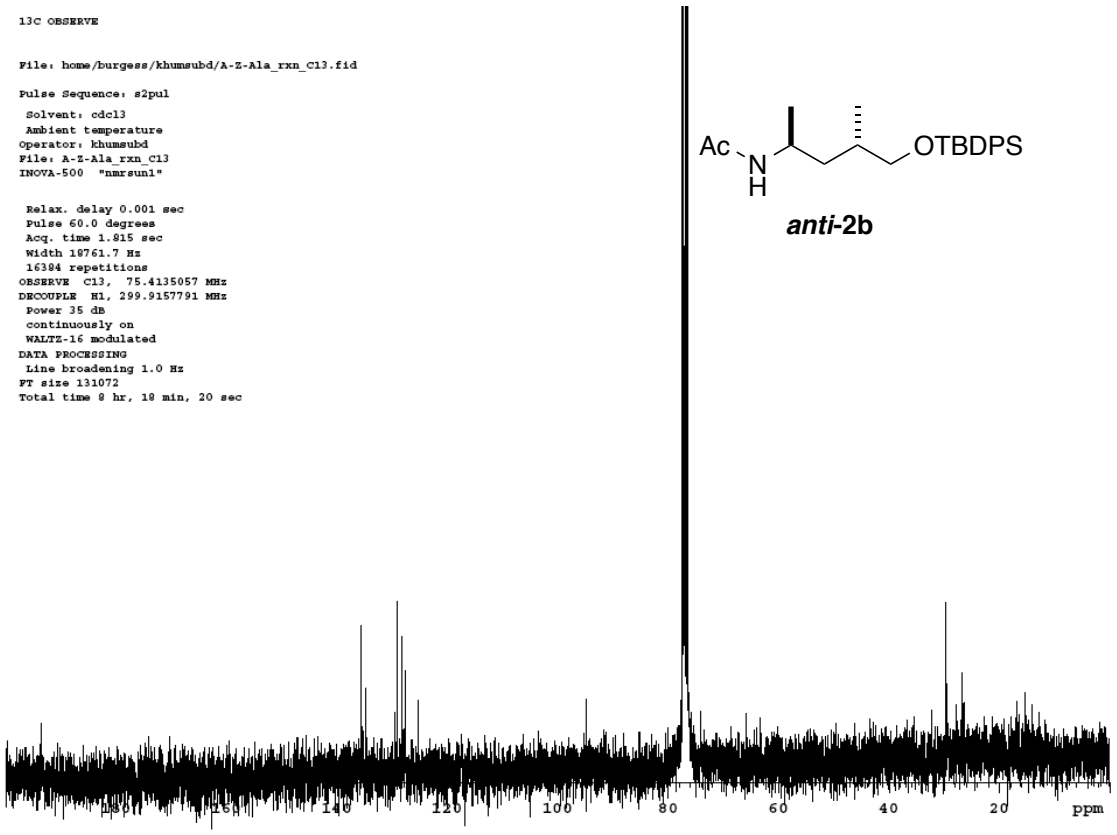

13C OBSERVE
File: home/burgess/yzhu/vnmrsys/data/III-ZY12-L-C13.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: yzhu
File: III-ZY12-L-C13
Mercury-300BB "mercury300"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
23000 repetitions
OBSERVE C13, 75.4135057 MHz
DECOUPLE H1, 299.9157791 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 13 hr, 30 min, 5 sec
Ac
N
H
OTBDPS
anti-2a
180
160
140
120
100
80
60
40
20
ppm



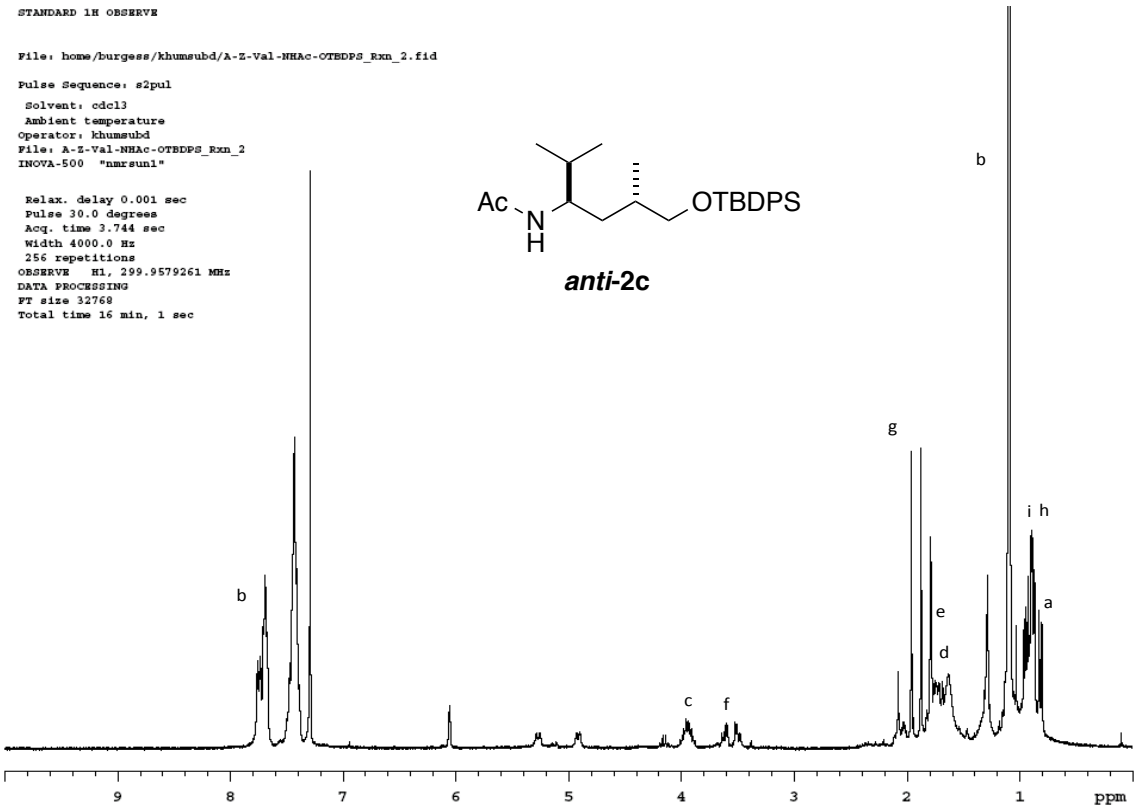
***anti*-2b**

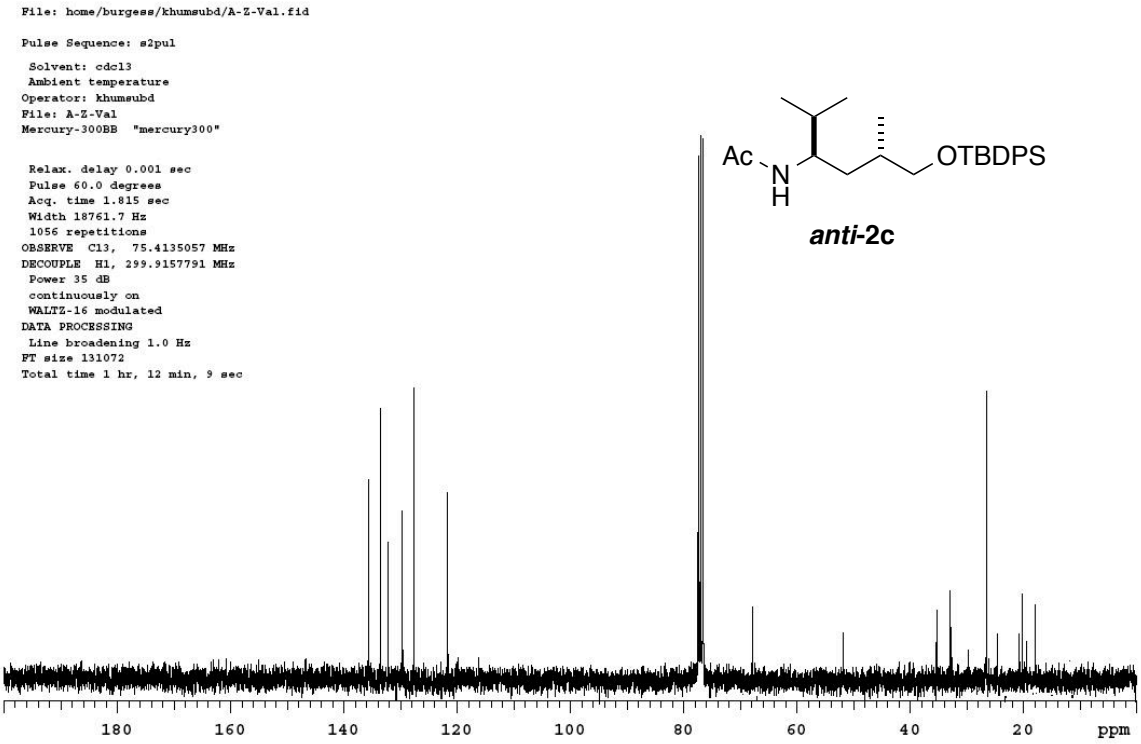
***N*-((2*S*,4*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*anti*-2b).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.63 (4H, m), 7.53-7.13 (6H, m), 4.10-3.95 (1H, m), 3.49-3.44 (2H, m), 2.60-2.51 (1H, m), 2.35 (3H, s), 1.97-1.62 (1H, m), 1.53 (3H, d, J = 6.0 Hz), 1.21 (3H, d, J = 9.0 Hz), 1.08 (9H, s), 0.97-0.79 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.8, 129.7, 129.0, 128.2, 124.6, 95.4, 29.7, 26.8, 17.8. HRMS (ESI): Exact mass calcd for $C_{24}H_{36}NO_2Si$ *ie* $[M+H]^+$ 398.2515 Found 398.2571.

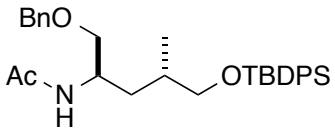




***N*-((3*R*,5*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhexan-3-yl)acetamide (*anti*-2c).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.69 (4H, m), 7.48-7.38 (6H, m), 4.92 (1H, d, *J* = 9.0 Hz), 3.98-3.91 (2H, m), 3.62-3.49 (2H, m), 1.96 (3H, s), 1.80-1.53 (2H, m), 1.40-1.20 (1H, m), 1.09 (9H, s), 0.96-0.81 (9H, m);^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.8, 133.6, 132.3, 129.9, 127.8, 122.0, 67.9, 51.7, 35.2, 32.1, 26.3, 24.5, 21.8, 20.7, 19.8, 18.0. HRMS (ESI): Exact mass calcd for $C_{26}H_{40}NO_2Si$ *ie* $[M+H]^+$ 426.2828. Found 426.2842.

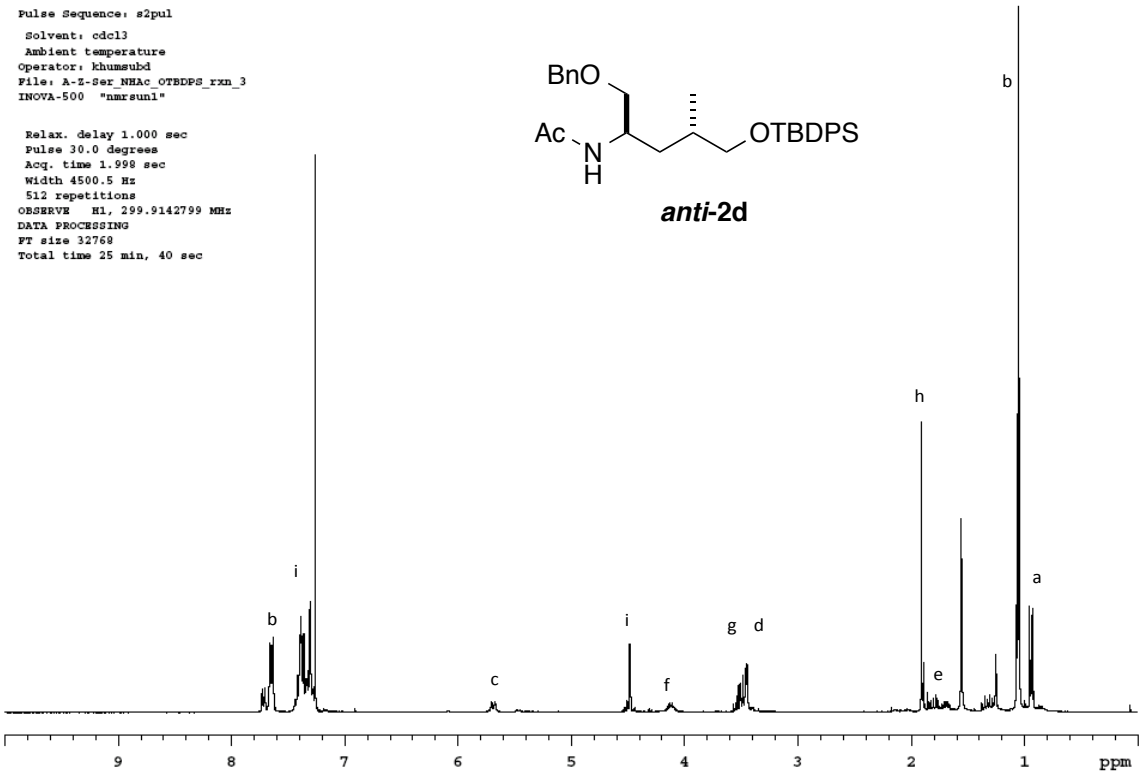

STANDARD 1H OBSERVE
File: home/burgess/khumsubd/A-Z-Val-NHAc-OTBDPS_Rxn_2.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-Z-Val-NHAc-OTBDPS_Rxn_2
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
256 repetitions
OBSERVE H1, 299.9579261 MHz
DATA PROCESSING
FT size 32768
Total time 16 min, 1 sec
Ac
N
H
OTBDPS
anti-2c
b
g
i h
e
d
a
c
f
9
8
7
6
5
4
3
2
1
ppm

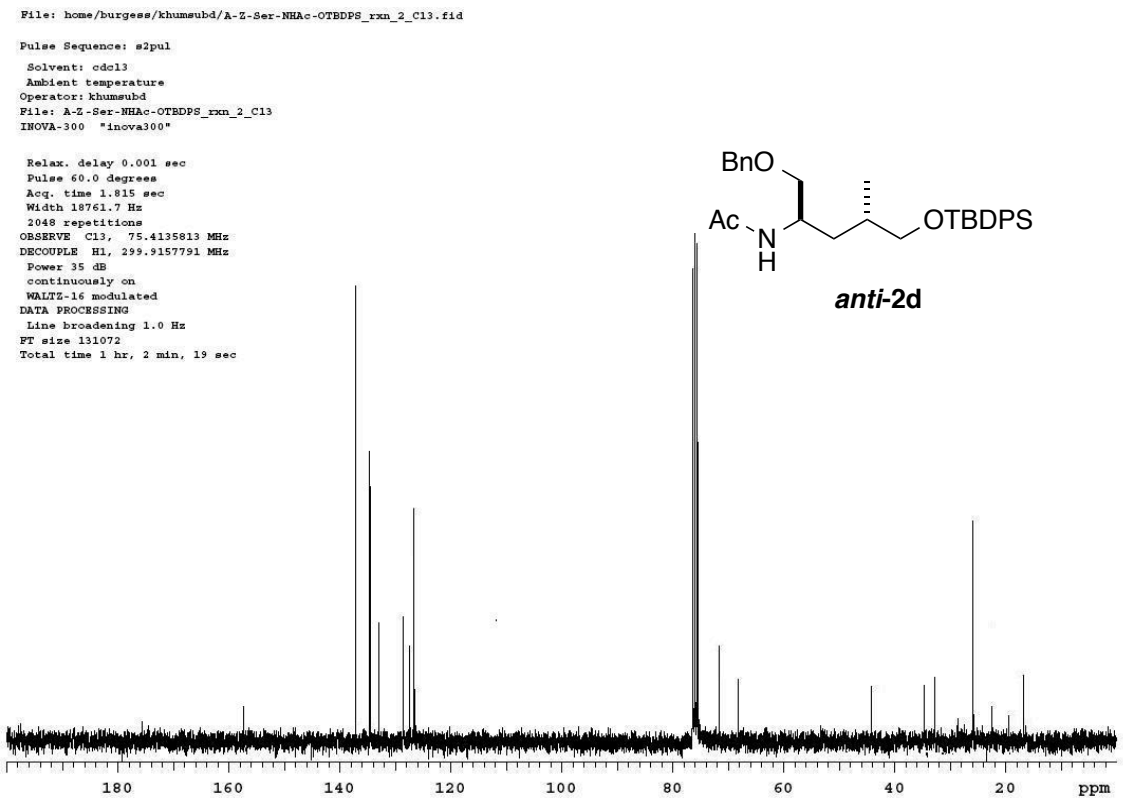

File: home/burgess/khumsubd/A-Z-Val.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-Z-Val
Mercury-300BB "mercury300"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1056 repetitions
OBSERVE C13, 75.4135057 MHz
DECOUPLE H1, 299.9157791 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 12 min, 9 sec
Ac
N
H
OTBDPS
anti-2c
180
160
140
120
100
80
60
40
20
ppm



***anti*-2d**

***N*-((2*R*,4*S*)-1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*anti*-2d).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.63 (4H, m), 7.47-7.30 (11H, m), 5.73 (1H, d, J = 8.1 Hz), 4.52 (2H, s), 4.17-4.14 (1H, m), 3.60-3.44 (4H, m), 1.94 (3H, s), 1.89-1.55 (2H, m), 1.37-1.32 (1H, m), 1.08 (9H, s), 0.97 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 137.2, 135.1, 134.5, 132.7, 128.5, 127.7, 127.3, 71.3, 68.1, 42.7, 34.7, 32.8, 26.0, 22.5, 19.8, 17.2. HRMS (ESI): Exact mass calcd for $C_{31}H_{42}NO_3Si$ *ie* $[M+H]^+$ 504.2934. Found 504.2971.





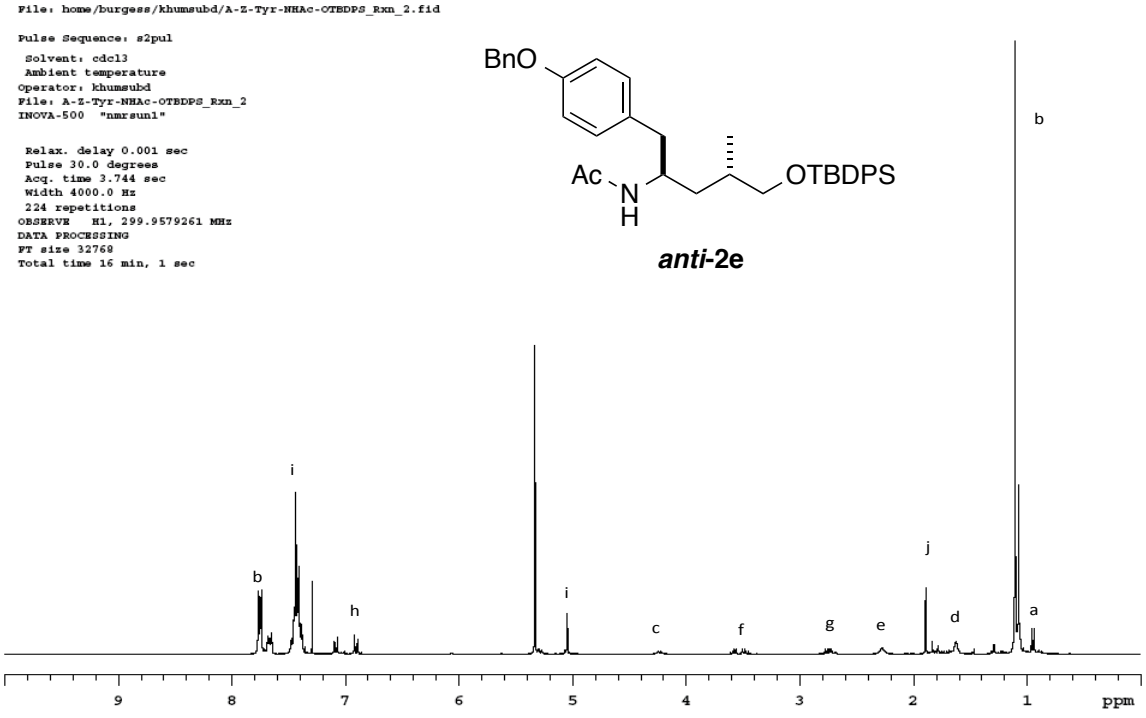
***anti*-2d**

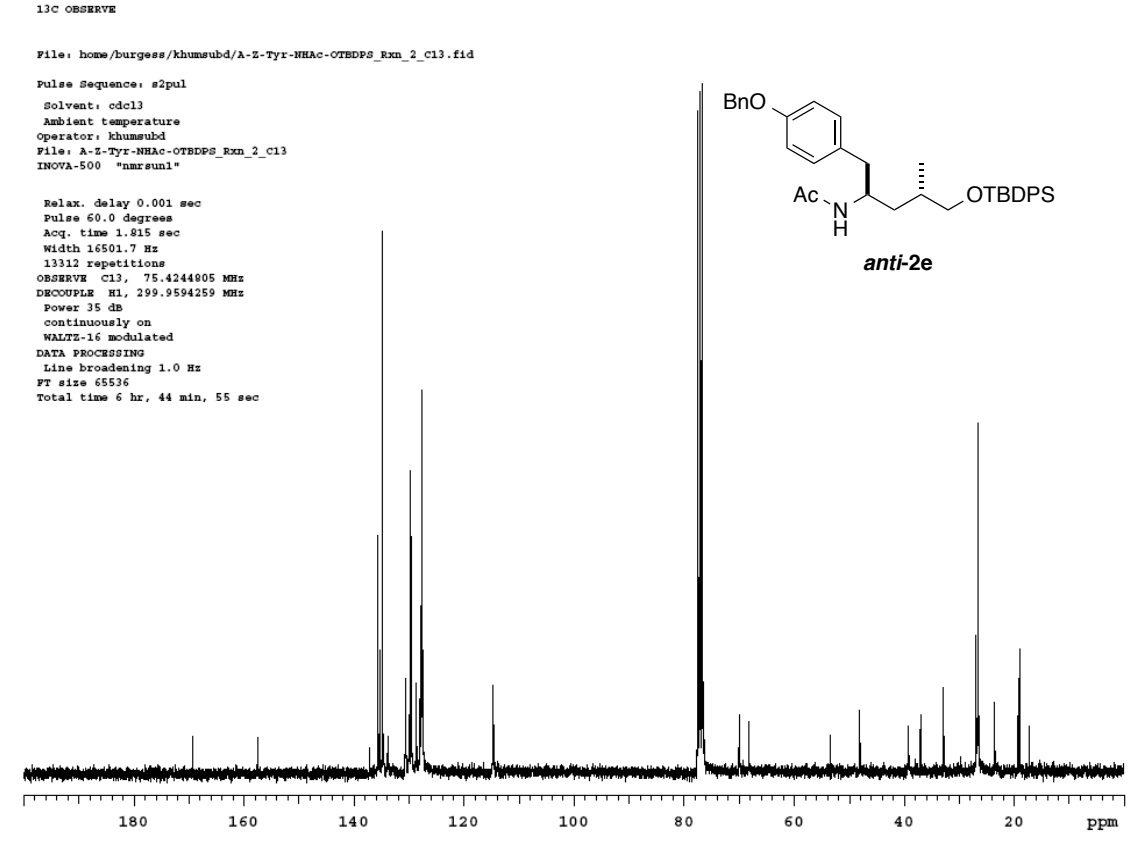
BnO

Ac N H OTBDPS

***anti*-2e**

_N_-((2_R_,4_S_)-1-(4-(Benzyloxy)phenyl)-5-((_tert_-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*anti*-2e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.66 (4H, m), 7.65-7.36 (11H, m), 7.08 (2H, dd, J = 9.0 Hz), 6.91 (2H, d, J = 8.7 Hz), 5.05 (2H, s), 4.25-4.18 (1H, m), 3.58-3.45 (1H, m), 2.78-2.72 (2H, m), 2.28 (2H, br), 1.89 (3H, s), 1.68-1.59 (1H, br), 1.11 (9H, s), 1.10 (2H, s), 0.95 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 137.1, 135.6, 135.3, 135.2, 134.8, 133.7, 130.0, 129.7, 128.6, 127.9, 127.8, 127.5, 121.1, 116.5, 114.7, 68.2, 53.5, 48.1, 39.2, 37.0, 32.8, 26.6, 23.5, 19.4, 17.2. HRMS (ESI): Exact mass calcd for $C_{37}H_{46}NO_3Si$ *ie* $[M+H]^+$ 580.3247. Found 580.3272.

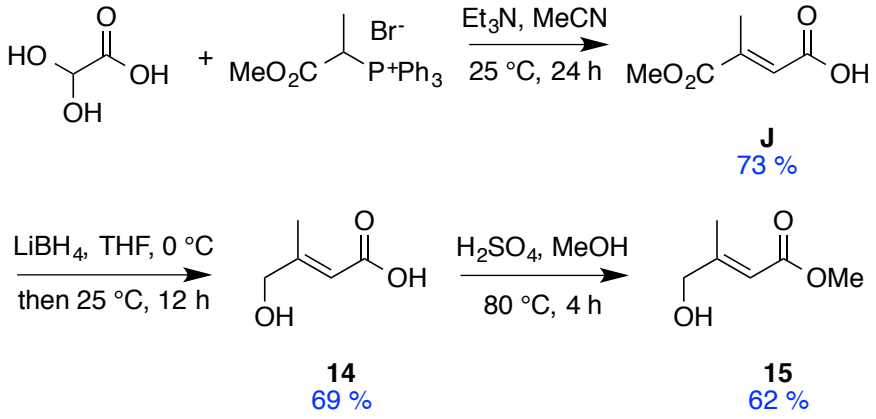

File: home/burgess/khumsubd/A-Z-Tyr-NHAc-OTBDPS_Rxn_2.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-Z-Tyr-NHAc-OTBDPS_Rxn_2
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 30.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
224 repetitions
OBSERVE H1, 299.9579261 MHz
DATA PROCESSING
FT size 32768
Total time 16 min, 1 sec
BnO
Ac
N
H
OTBDPS
anti-2e
b
i
h
c
f
g
e
j
d
a
9
8
7
6
5
4
3
2
1
ppm


13C OBSERVE
File: home/burgess/khumsubd/A-Z-Tyr-NHAc-OTBDPS_Rxn_2_C13.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: khumsubd
File: A-Z-Tyr-NHAc-OTBDPS_Rxn_2_C13
INOVA-500 "nmrsun1"
Relax. delay 0.001 sec
Pulse 60.0 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
13312 repetitions
OBSERVE C13, 75.4244805 MHz
DECOUPLE H1, 299.9594259 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 6 hr, 44 min, 55 sec
BnO
Ac
N
H
OTBDPS
anti-2e
180
160
140
120
100
80
60
40
20
ppm

APPENDIX C
EXPERIMENTAL FOR CHAPTER III

A. Preparation of compounds 15

Preparation of (*E*)-Methyl 4-Hydroxy-3-methylbut-2-enoate 15.



(*E*)-4-Methoxy-3-methyl-4-oxobut-2-enoic acid (J)[139];

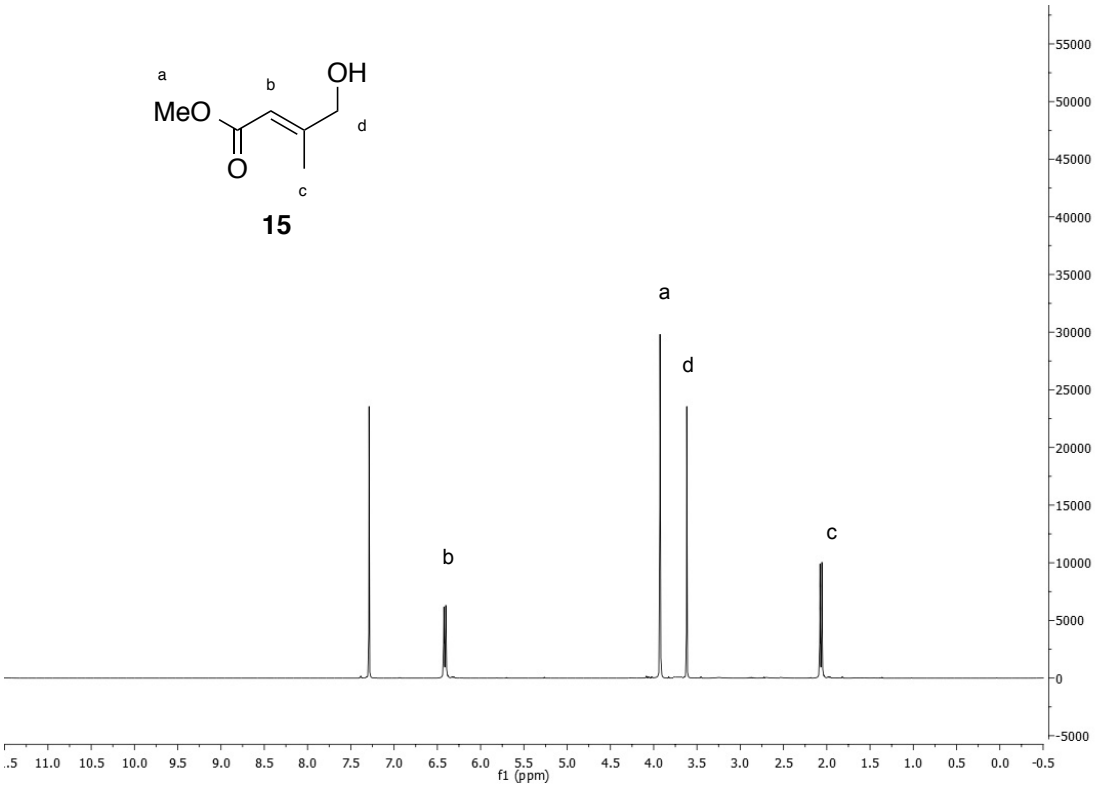
To a solution of (1-methoxy-1-oxopropan-2-yl)triphenylphosphonium bromide (42.9 g, 100 mmol, 1 equiv) in dry MeCN (300 mL) was added triethylamine (13.2 mL, 95 mmol, 0.95 equiv) and glyoxylic acid monohydrate (8.74 g, 95 mmol, 0.95 equiv) at 0 °C. The solution was further stirred at 0 °C for 2 h and at room temperature overnight. Half of the solvent was removed under reduced pressure, and ethyl acetate (100 mL) was added. The resulting solution was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 50 mL), acidified (pH 1 - 2) at 0 °C with concentrated HCl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were evaporated to dryness, yielding a clear oil **J** (10.5 g, 73 %) which was used for the next reaction without further purification.

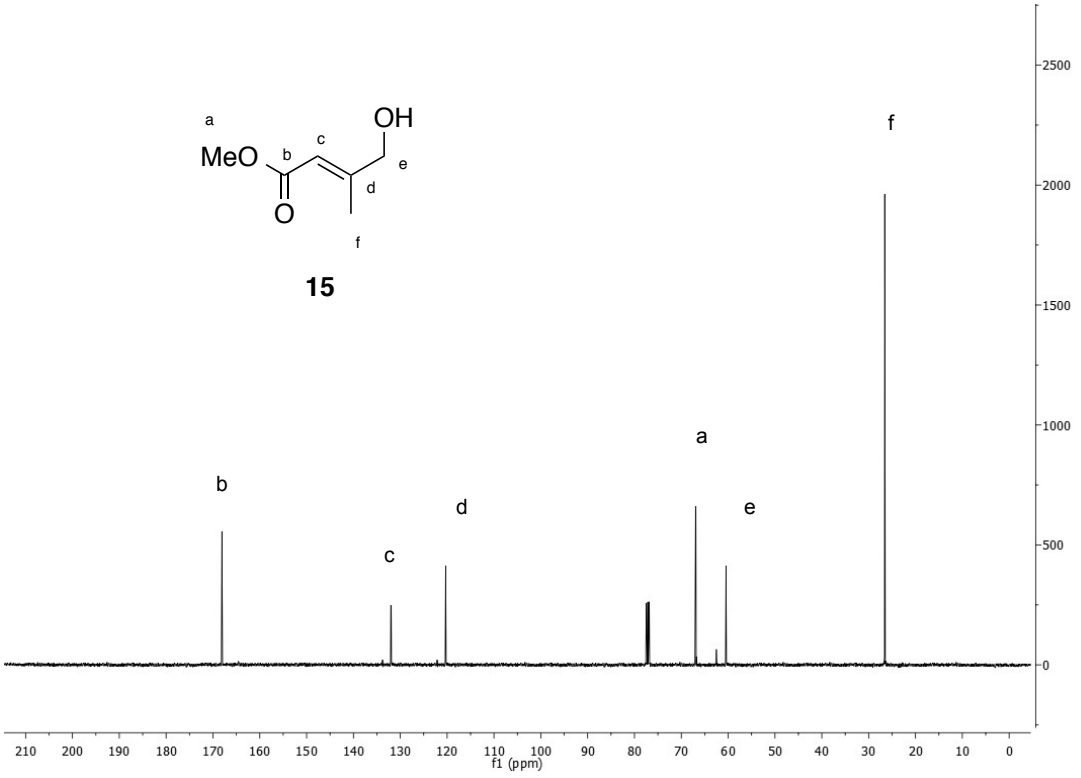
(*E*)-4-Hydroxy-3-methylbut-2-enoic acid (14)[140]**;**

$LiBH_4$ (2 equiv) was added to (*E*)-4-methoxy-3-methyl-4-oxobut-2-enoic acid **J** (200 mmol) in THF (200 mL) at 0 °C. The reaction mixture was then allowed to ambient temperature and stirred for 12 h. The mixture was poured into 1N HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed under reduced pressure to yield the product **14** as a white solid (16 g, 69 %) which was used for the next reaction without further purification.

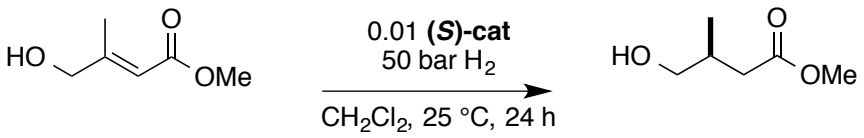
(*E*)-Methyl 4-Hydroxy-3-methylbut-2-enoate (15);

To a solution of H_2SO_4 in 50 mL of MeOH, (*E*)-4-hydroxy-3-methylbut-2-enoic acid **14** was added at room temperature. The mixture was stirred and refluxed for 4 h. After cooling to ambient temperature, solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to obtain product **15** as a clear oil (62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, d, J = 4.7 Hz), 3.96 (2H, s), 3.63 (3H, s), 1.89 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 132.3, 119.7, 67.2, 58.3, 26.2. HRMS (ESI): Exact mass calcd for $C_6H_{11}O_3$ *ie* $[M+H]^+$ 131.0708. Found 131.0711.


a
b
OH
MeO
d
O
c
15
a
d
b
c
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


a
OH
c
MeO
b
e
d
O
f
15
f
b
a
d
e
c
2500
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

B. Catalytic Hydrogenation conditions

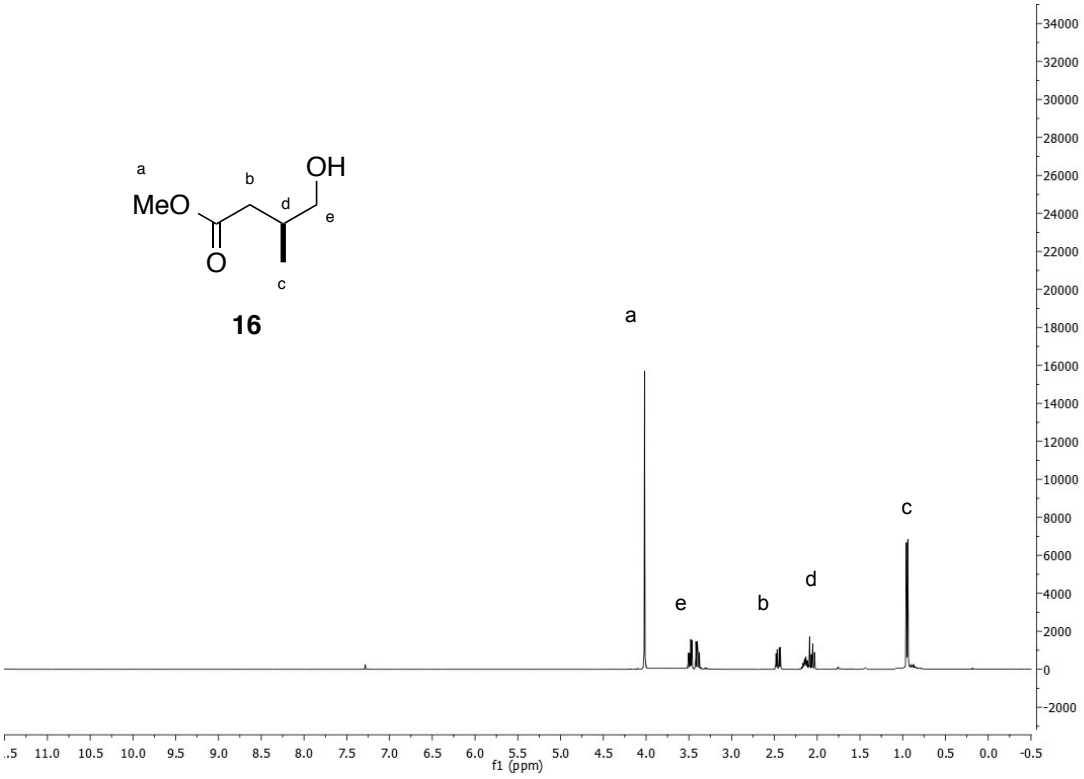


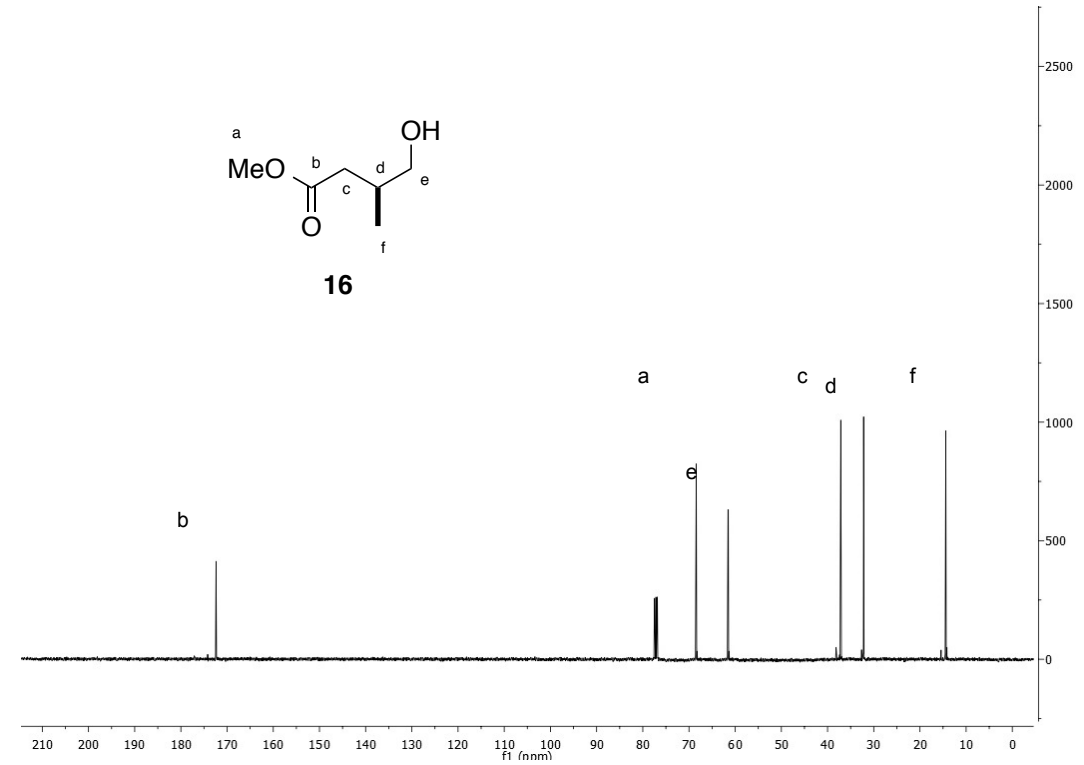
15 **16**
100 %
crude 94 % *ee*

The (*E*)-Methyl 4-hydroxy-3-methylbut-2-enoate **15** (100 mmol) and **(*S*)-1** (1 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 24 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 10 - 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC analysis.

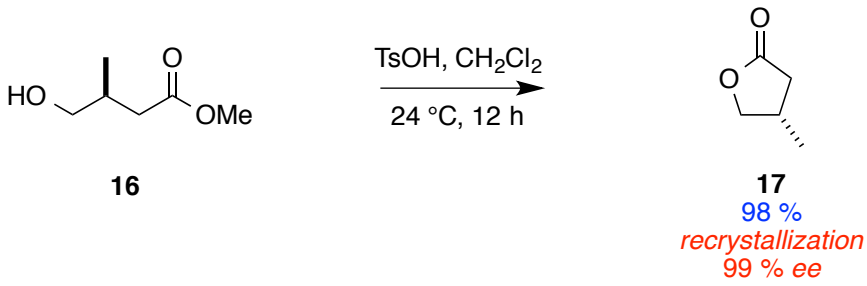
Methyl (*S*)-4-Hydroxy-3-methylbutanoate (16);

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (3H, s), 3.35 (2H, dd, J = 6.6, 12 Hz), 2.48 (2H, m), 2.07 (1H, m), 0.92 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 68.5, 62,1, 37.8, 32.5, 14.7. HRMS (ESI): Exact mass calcd for $C_6H_{13}O_3$ *ie* $[M+H]^+$ 133.0865. Found 133.0864.


a
b
OH
MeO
d
e
O
c
16
a
c
d
e
b
f1 (ppm)


a
OH
MeO
b
d
c
e
O
f
16
a
c
d
f
e
b
f1 (ppm)

C. Preparation of (*S*)-4-Methyldihydrofuran-2(3*H*)-one (17).



16 **17**
98 %
recrystallization
99 % *ee*

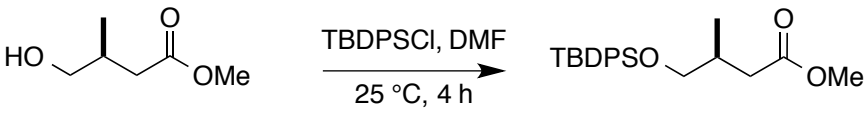
To a solution of methyl (*S*)-4-hydroxy-3-methylbutanoate **16** in 30 mL of CH_2Cl_2, TsOH (0.95 equiv) was added at room temperature. The mixture was stirred for 6 h, then the organic layer was washed with H_2O (3 × 30 mL), brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to yield product as colorless oil (98 %).

D. Recrystallization conditions

(*S*)-4-Methyldihydrofuran-2(3*H*)-one **17** was dissolved in EtOAc and hexane and the mixture was cooled to -20 °C. After getting precipitation, solvent was decanted in low temperature and washed with cold hexane.

E. Preparation of compounds 18

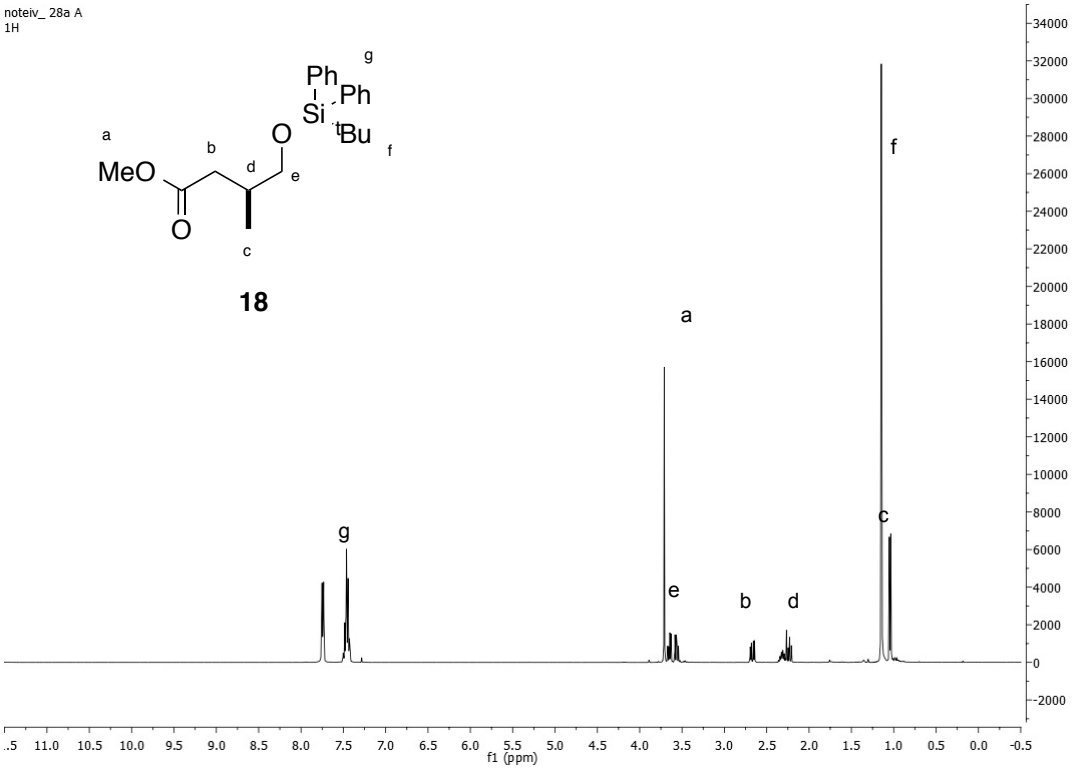
Preparation of Methyl (*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbutanoate (18).

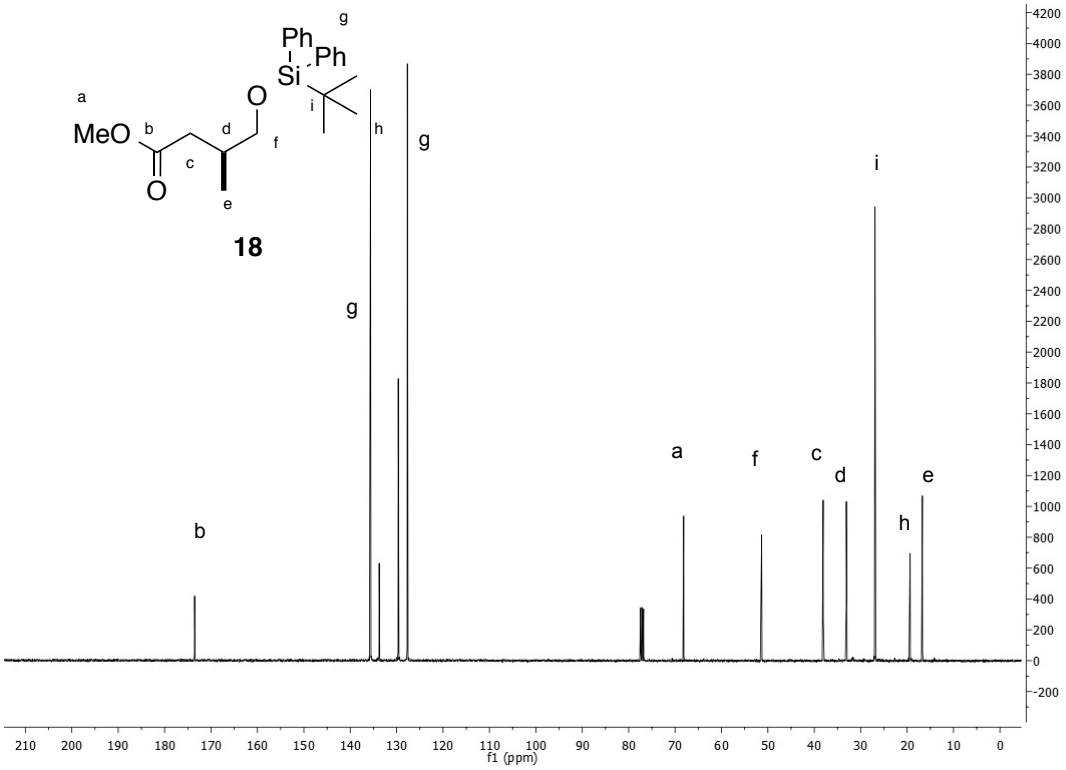


16 **18**
99 %

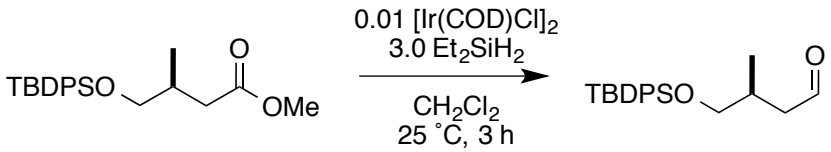
To a solution of methyl (*S*)-4-hydroxy-3-methylbutanoate **3** in 30 mL of DMF, TBDPSCl (0.95 equiv) was added at room temperature. The mixture was stirred for 4 h, then solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O (3 × 30 mL), brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude was purified by

chromatography using 5 % EtOAc/hexane as eluent to obtain product **5** as a clear oil (15 g, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.30 (10H, m), 3.69 (3H, s), 3.59 (2H, dd, *J* = 3.3, 12 Hz), 2.63-2.60 (2H, m), 2.32-2.20 (1H, m), 1.09 (9H, s), 1.02 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.8, 133.8, 129.7, 126.9, 68.7, 51.9, 38.7, 26.8, 19.7, 16.1. HRMS (ESI): Exact mass calcd for $C_{22}H_{31}O_3Si$ *ie* $[M+H]^+$ 371.0242. Found 371.0222.





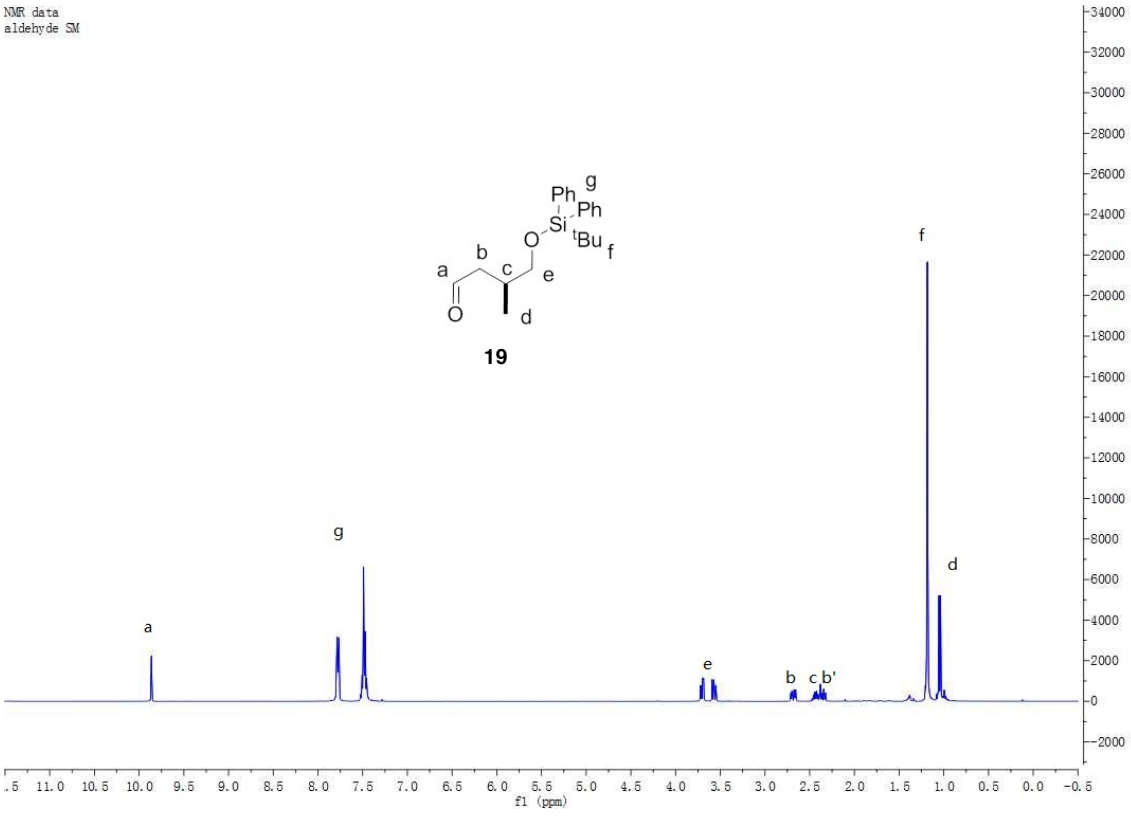
F. Preparation of (*S*)-4-*(tert*-Butyldiphenylsilyloxy)-3-methylbutanal (19).

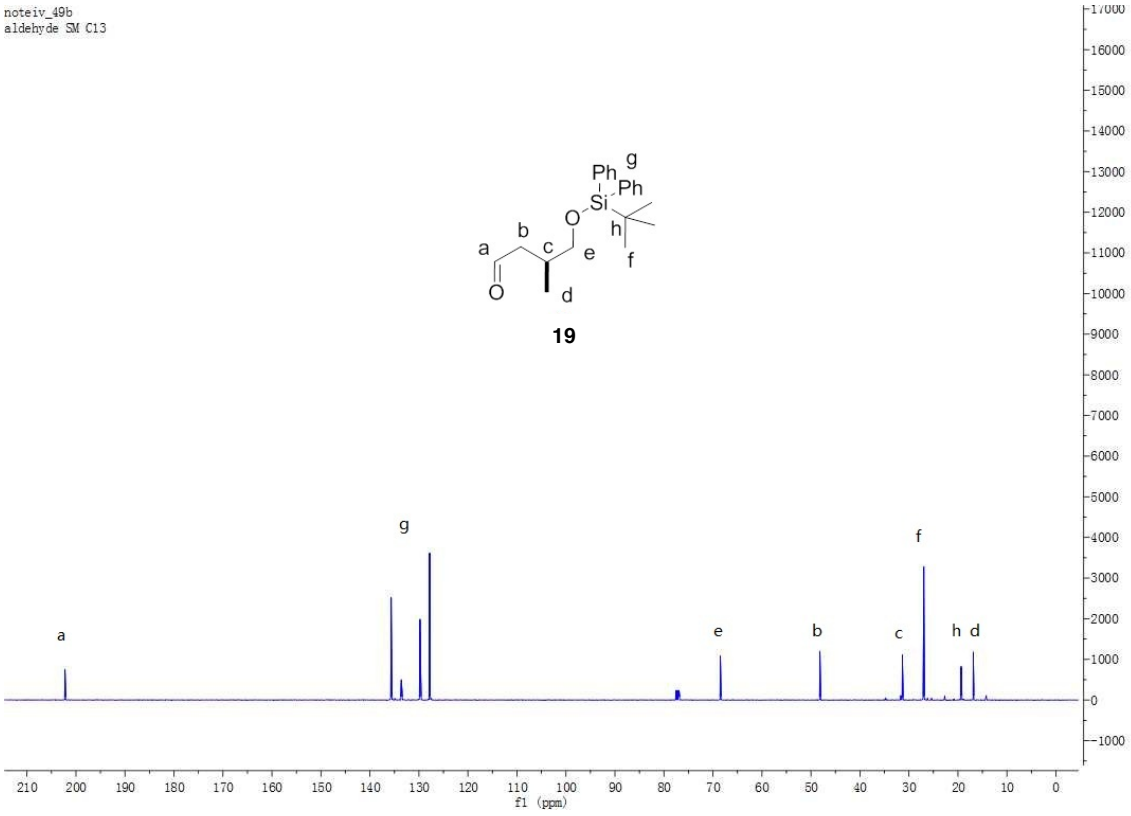


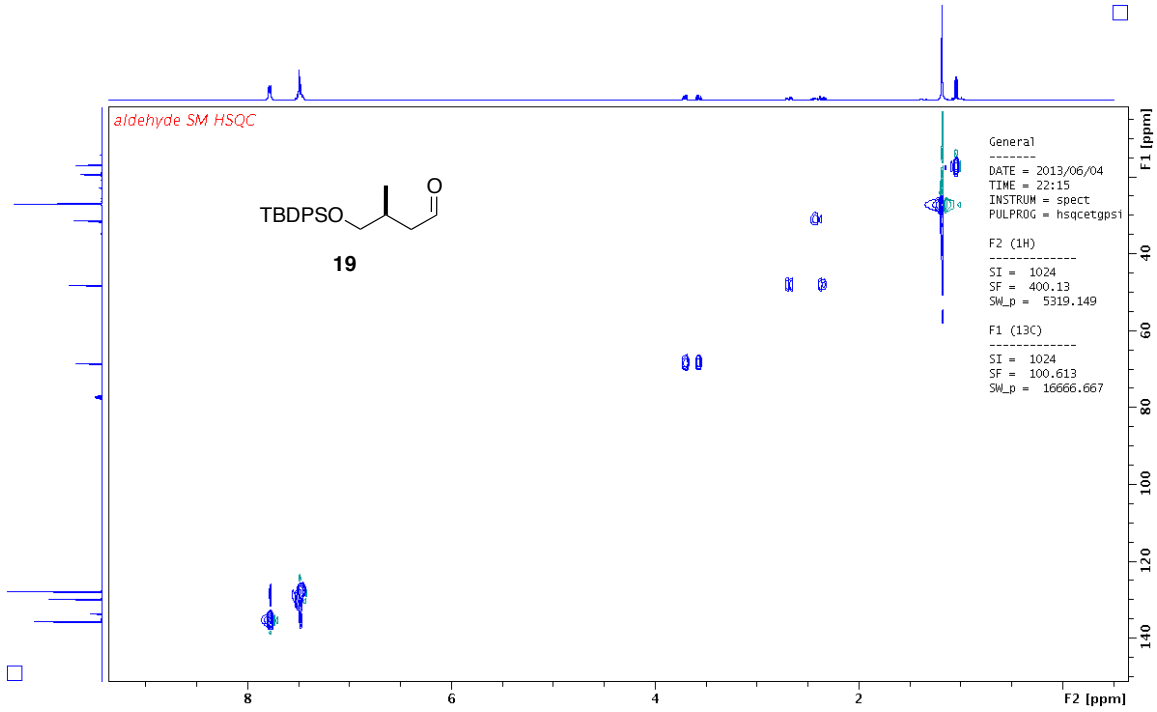
18 **19**
75 %

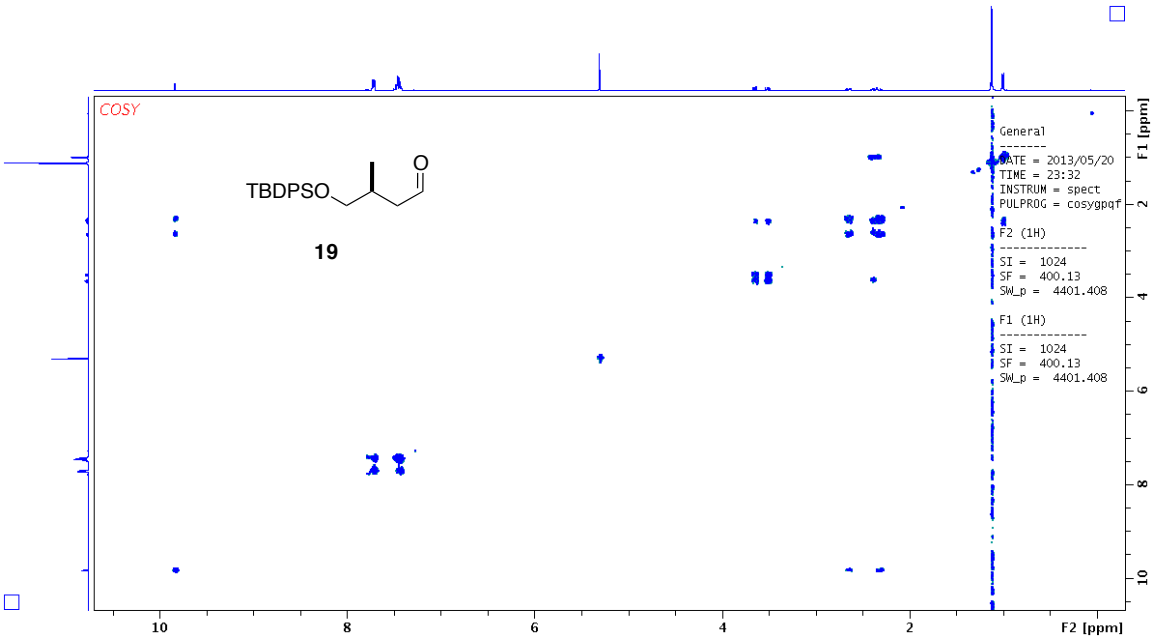
A modification of reported procedure[144] was used. Under an atmosphere of argon, to an oven dried flask was added $[Ir(COD)Cl]_2$ (10.1 mg, 0.015 mmol) and 1.5 mL of CH_2Cl_2. Then diethyl silane (529 mg, 6 mmol) was added and the resulting mixture was stirred at 23 °C for 1 minute. After addition of methyl (*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutanoate **18** (3 mmol), the mixture was stirred at 23 °C for 1 h. Then add another portion of $[Ir(COD)Cl]_2$ (10.1 mg, 0.015 mmol) and diethyl silane (265 mg, 3 mmol) to the mixture and allow it to stir 23 °C for 2 h. The reaction was diluted with diethyl ether and quenched by 0.1 M HCl. After stirring for 20 minutes, the layers were separated and the aqueous layer was extracted with CH_2Cl_2.

The combined organic layers were dried with $MgSO_4$, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel using 10 % ~ 15 % CH_2Cl_2/hexanes as eluents gave the desired aldehyde **19** as colorless oil (766 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (1H, t, *J* = 2.1 Hz), 7.81 – 7.74 (4H, m), 7.54 – 7.47 (6H, m), 3.70 (1H, dd, *J* = 9.9, 5.1 Hz), 3.57 (1H, dd, *J* = 9.9, 6.9 Hz), 2.69 (1H, ddd, *J* = 15.9, 5.7, 2.1 Hz), 2.48 – 2.39 (1H, m), 2.35 (1H, ddd, *J* = 15.9, 7.2, 2.1 Hz), 1.18 (9H, s), 1.05 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 135.6, 135.6, 133.6, 133.5 129.8, 127.8, 68.5, 48.2, 31.3, 27.0, 19.3, 16.9. IR (CH_2Cl_2) n (cm^{-1}) 3070, 2931, 2858, 2360, 1724, 1469, 1427, 1111, 806.3, 740.7, 702.1. HRMS (ESI): Exact mass calcd for $C_{21}H_{28}O_2SiLi$ *ie* $[M+Li]^+$ 347.2019. Found 347.2021.

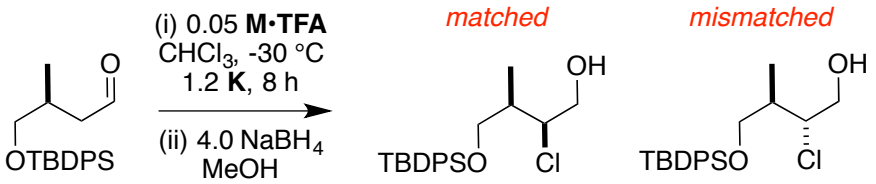



noteiv_49b
aldehyde SM C13
Ph
Ph
Si
O
a
b
c
d
e
f
g
h
O
19
a
g
e
b
c
f
h d
f1 (ppm)


aldehyde SM HSQC
TBDPSO
O
19
General
DATE = 2013/06/04
TIME = 22:15
INSTRUM = spect
PULPROG = hsqcetgpsi
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 5319.149
F1 (13C)
SI = 1024
SF = 100.613
SW_p = 16666.667
F1 [ppm]
F2 [ppm]



G. Typical Procedure for α-Chlorination of the Aldehyde.



19

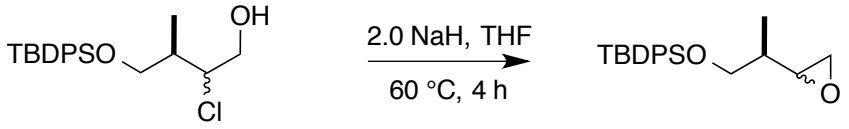
syn-**20**
(*S*)-M•TFA
78 %
syn:anti
18:1.0

anti-**20**
(*R*)-M•TFA
75 %
syn:anti
1.0:10

A modification of reported procedure[150] was used. 5-Benzyl-2,2,3,-trimethylimidazolidin-4-one trifluoroacetic acid salt (13.5 mg, 0.05 mmol) in chloroform (1 mL) is cooled to -30 °C for five minutes prior to addition of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (181 mg, 0.6 mmol). The aldehyde **19** (170 mg, 0.5 mmol) was added to the yellow mixture. The resulting mixture was stirred at -30 °C for 8 h. The reaction was then warmed to 0 °C and MeOH (1 mL) was added to the mixture, followed by $NaBH_4$ (80 mg, 2 mmol). After stirring at 0 °C for 5 minutes, the reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*.

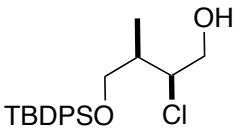
Purification of the residue by flash chromatography on silica gel, eluting with 2.5 % ~ 5.0 % EtOAc/hexanes gave the desired alcohol as colorless oil.

H. Typical Procedure for Preparation Epoxides.



20 **23**

Under Ar, to a solution of **20** (75.4 mg, 0.2 mmol) in anhydrous THF was added NaH (10.0 mg, 0.4 mmol) and the mixture was stirred at 60 °C for 4 h. The reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with CH_2Cl_2 three times. The combined organic layers were dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, eluting with CH2Cl2/hexanes (20 %) gave the desired epoxide as a colorless oil.



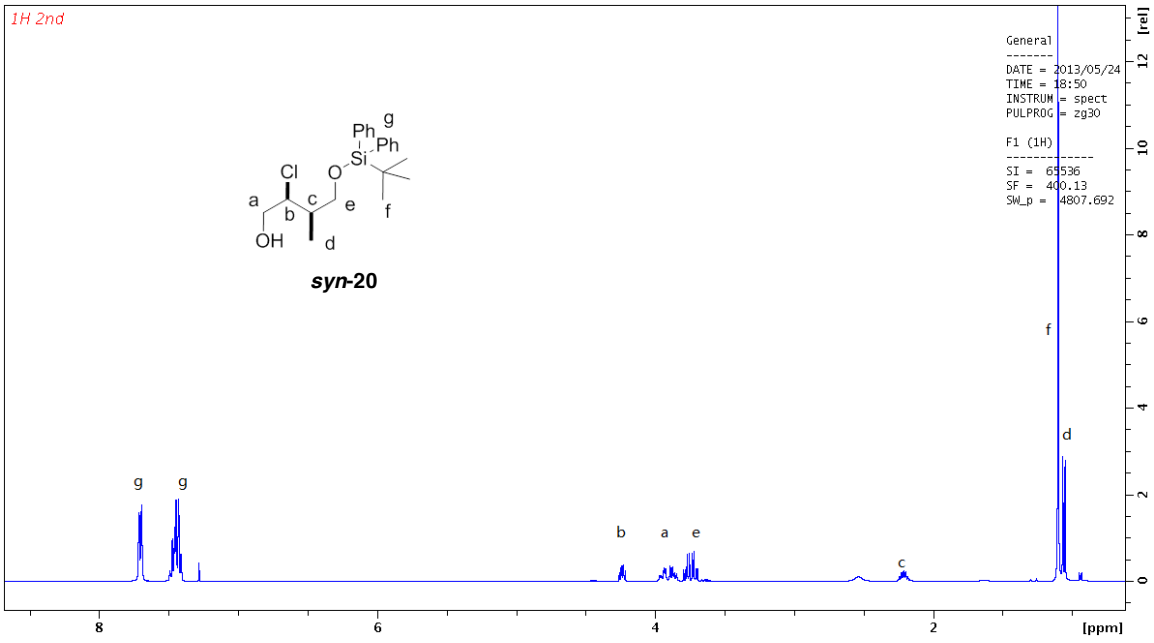
syn-**20**

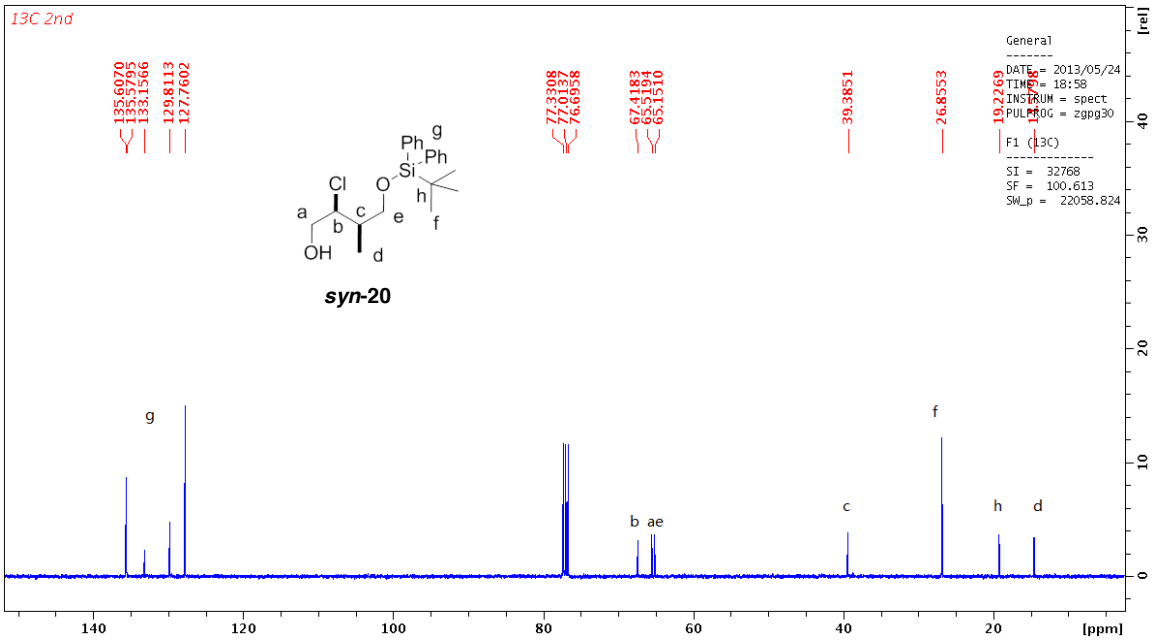
(2*S*,3*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-chloro-3-methylbutan-1-ol (*syn*-20);

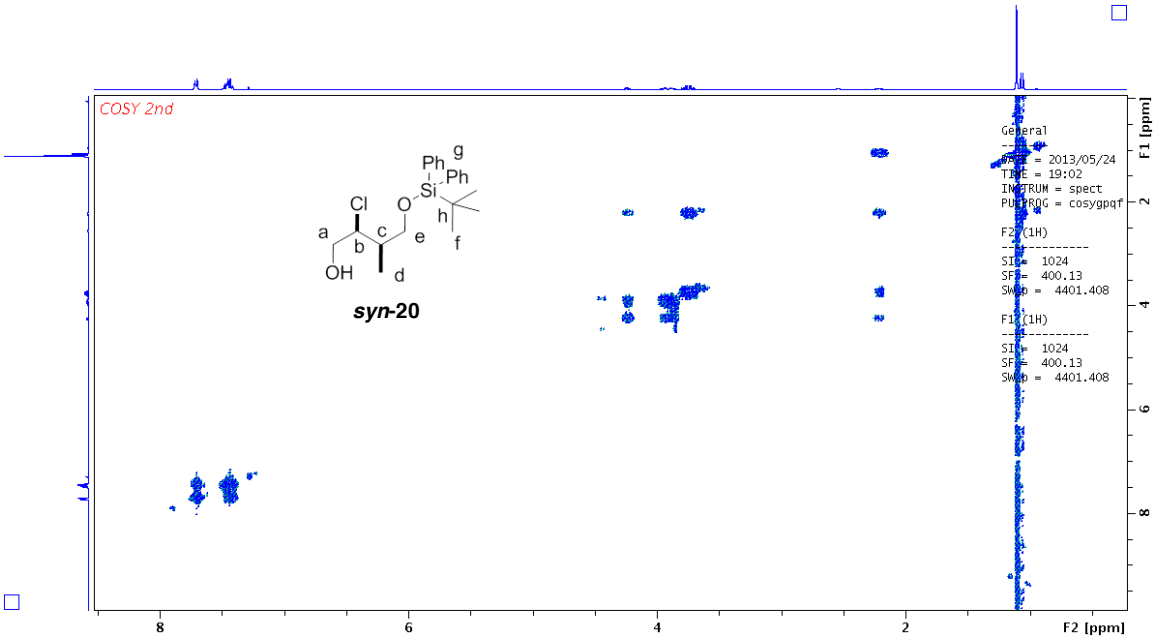
The compound was prepared according to the typical α-chlorination procedure catalysed by (*S*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one trifluoroacetic acid salt. Purification by flash chromatography afforded *syn*-**20** as a colorless oil (147 mg, 78 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (4H, m), 7.54 – 7.44 (6H, m), 4.49 – 4.45 (1H, m), 3.88 – 3.86 (2H, m), 3.71 – 3.62 (2H, m), 2.34 (1H, br), 2.22 – 2.16 (1H, m), 1.12 (9H, s), 1.05 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.6, 133.2, 129.8, 127.8, 66.5, 65.7, 65.7, 38.8, 26.9, 19.3, 11.8. IR (CH_2Cl_2) n (cm^{-1}) 3356, 3071, 2932, 2859, 2361, 1470, 1427, 1377, 1111, 822. HRMS (ESI): Exact mass calcd for $C_{21}H_{30}ClO_2Si$ *ie* $[M+H]^+$ 377.1704. Found 377.1718. The diastereoselectivity

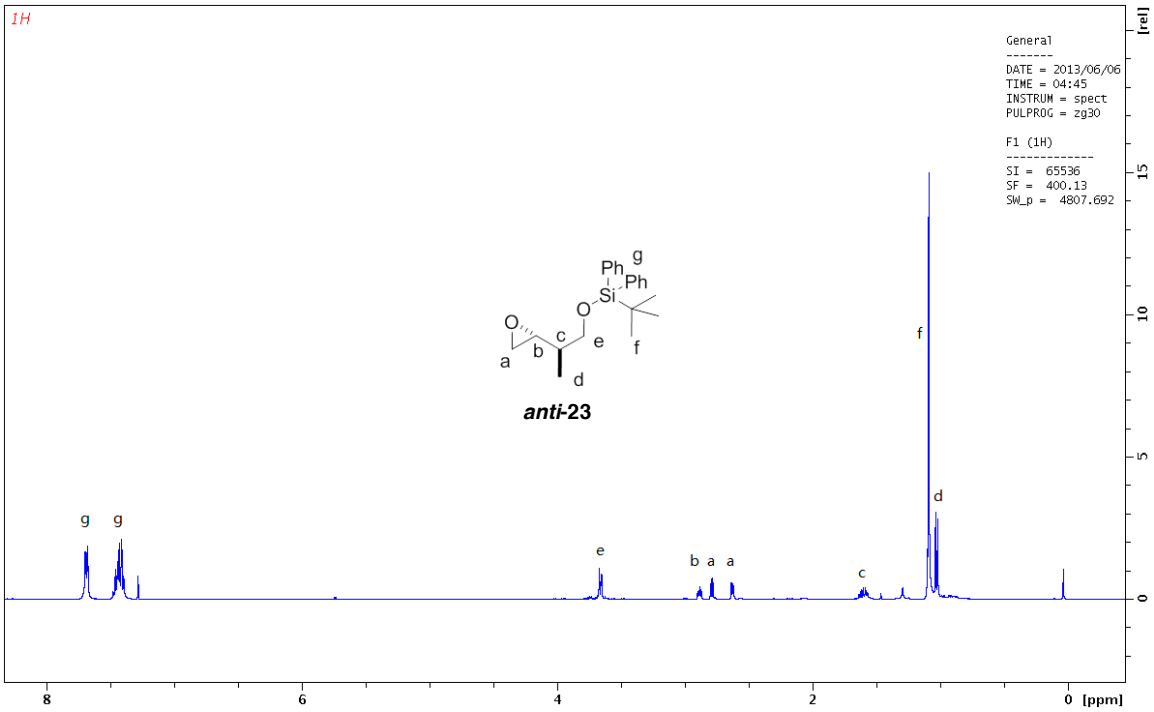
was 18:1.0, determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 11.7 min (major diastereomer), t_r 12.7 min (minor diastereomer).

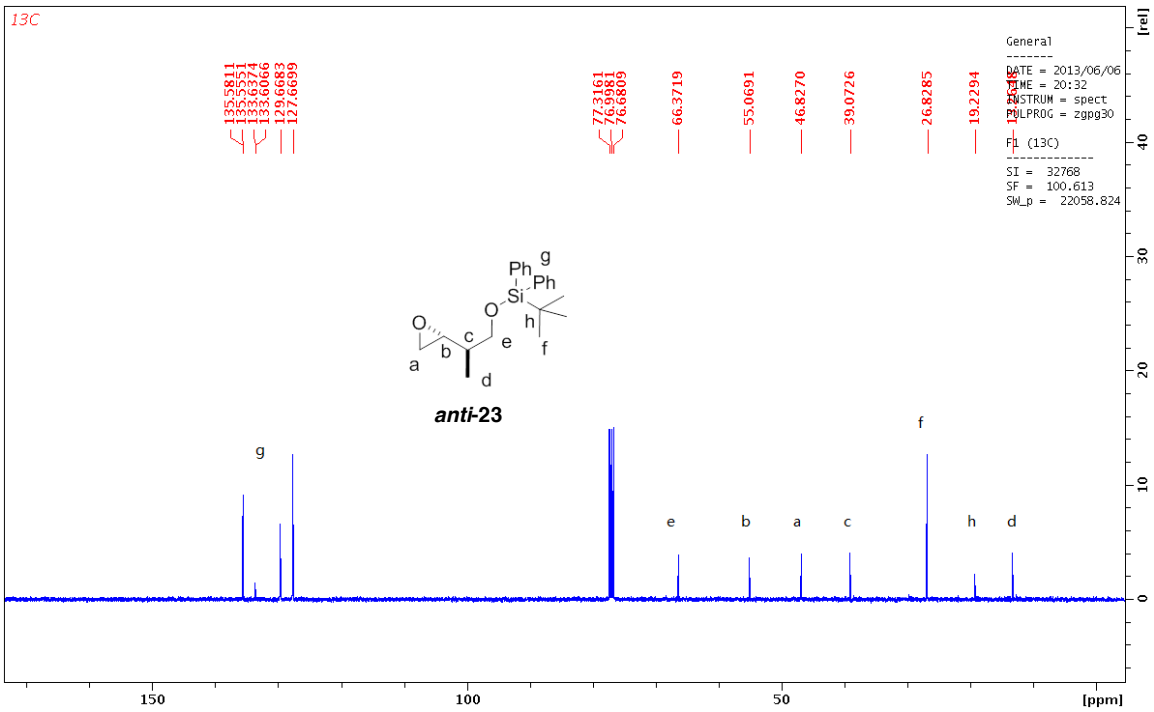
The product was converted to the epoxide according to the typical procedure for preparation epoxides. Purification by flash chromatography afforded (2*R*,3*R*)-4-*tert*-butyldiphenylsilyloxy-1,3-epoxy-3-methylbutane (*anti*-**23**) as a colorless oil (67.5 mg, 95 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.67 (4H, m), 7.49 – 7.38 (6H, m), 3.66 (2H, dd, *J* = 6.3, 1.6 Hz), 2.90 – 2.87 (1H, m), 2.79 (1H, dd, *J* = 4.9, 4.1 Hz), 2.63 (1H, dd, *J* = 5.0, 2.8 Hz), 1.65 – 1.56 (1H, m), 1.09 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.6, 129.7, 127.7, 66.4, 55.1, 46.8, 39.1, 26.8, 19.2, 13.3. IR (CH_2Cl_2) n (cm^{-1}) 3070, 2927, 2859, 2338, 1462, 1427, 1389, 1362, 1111, 933.6, 887.3, 821.7. HRMS (ESI): Exact mass calcd for $C_{21}H_{28}O_2SiLi$ *ie* $[M+Li]^+$ 347.2019. Found 347.2020.

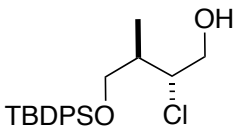



13C 2nd
135.6070
135.5795
133.1566
129.8113
127.7602
77.3308
77.0137
76.6958
67.4183
65.5194
65.1510
39.3851
26.8553
19.2269
17.7655
General
DATE = 2013/05/24
TIME = 18:58
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
syn-20
g
f
b ae
c
h
d
[rel]
[ppm]


COSY 2nd
General
DATE = 2013/05/24
TIME = 19:02
INSTRUM = spect
PULPROG = cosygpqf
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 4401.408
F1 (1H)
SI = 1024
SF = 400.13
SW_p = 4401.408
syn-20
F1 [ppm]
F2 [ppm]


1H
General
DATE = 2013/06/06
TIME = 04:45
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 400.13
SW_p = 4807.692
anti-23
g g
e
b a a
c
f
d
[rel]
[ppm]


13C
135.5811
135.5551
133.8274
133.6066
129.6683
127.6899
77.3161
76.9981
76.6809
66.3719
55.0691
46.8270
39.0726
26.8285
19.2294
General
DATE = 2013/06/06
TIME = 20:32
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
anti-23
g
e
b
a
c
f
h
d
[rel]
[ppm]



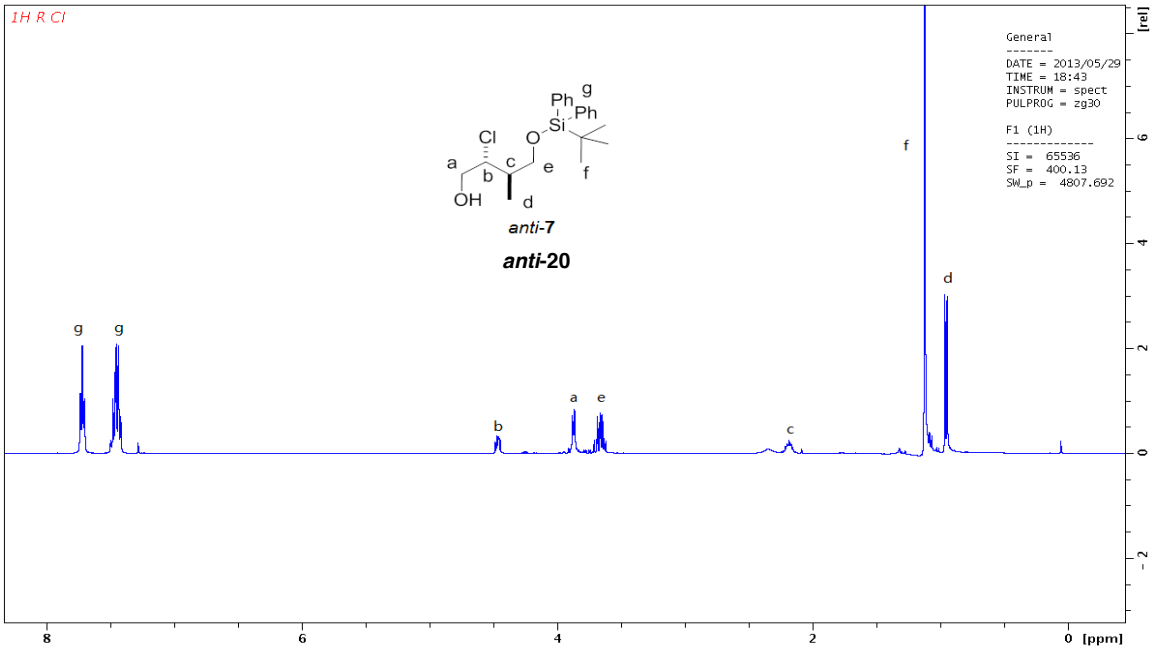
anti-**20**

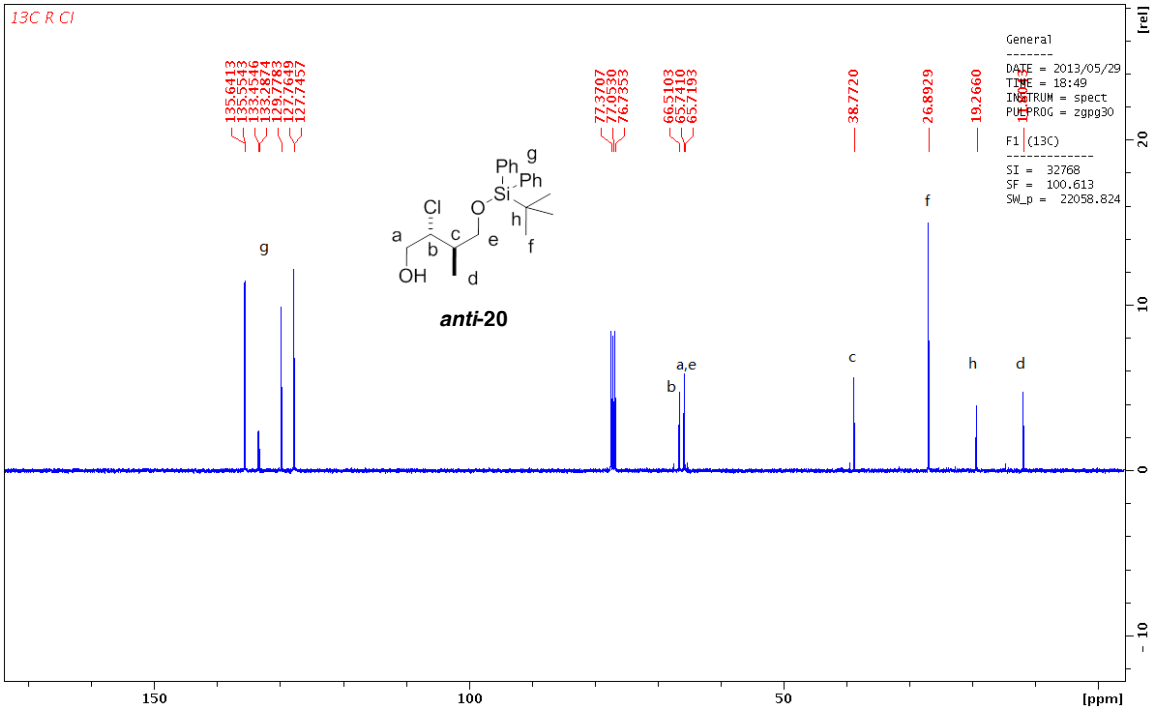
(2*R*,3*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-chloro-3-methylbutan-1-ol (*anti*-20);

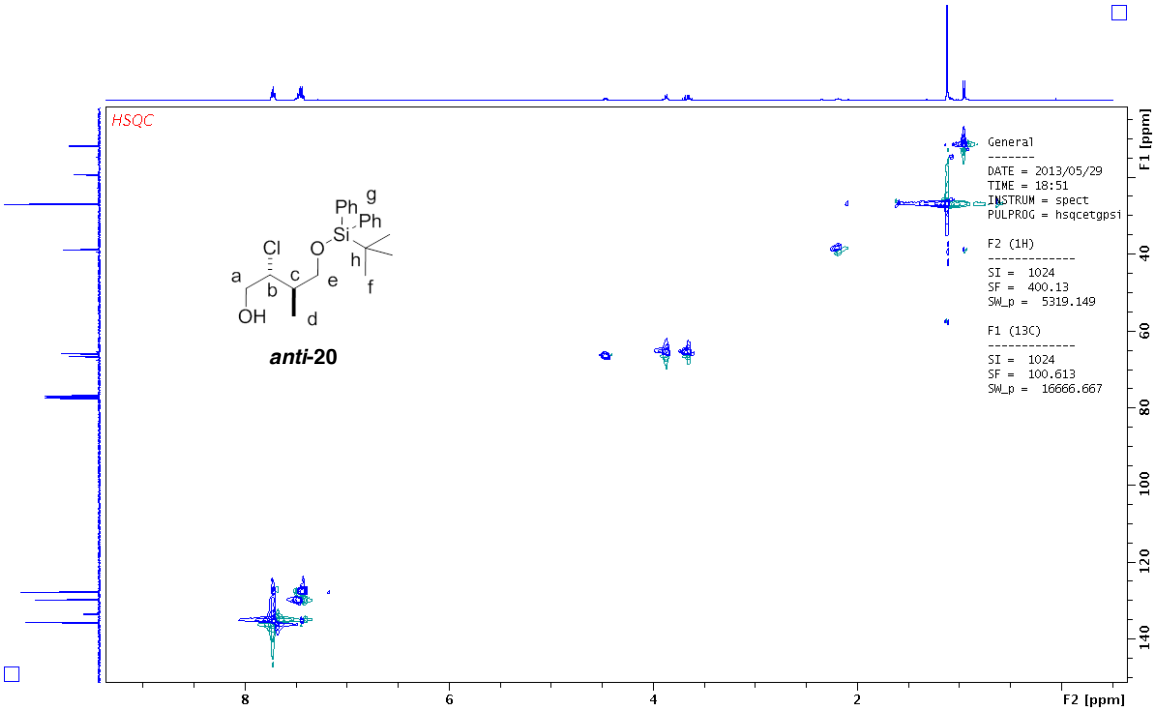
The compound was prepared according to the typical chlorination procedure catalysed by (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one trifluoroacetic acid salt. Purification by flash chromatography afforded *anti*-**7** as a colorless oil (141 mg, 75 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (4H, m), 7.51 – 7.39 (6H, m), 4.26 – 4.22 (1H, m), 3.95 (1H, dd, *J* = 12.2, 4.5 Hz), 3.87 (1H, dd, *J* = 12.2, 6.5 Hz), 3.78 (1H, dd, *J* = 10.4, 5.9 Hz), 3.72 (1H, dd, *J* = 10.4, 4.3 Hz), 2.54 (1H, br), 2.27 – 2.16 (1H, m), 1.10 (2H, s), 1.06 (1H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.1, 129.8, 127.8, 67.4, 65.5, 65.1, 39.4, 26.9, 19.2, 14.6. IR (CH_2Cl_2) n (cm^{-1}) 3383, 3071, 2932, 2859, 2361, 1470, 1427, 1389, 1111. HRMS (ESI): Exact mass calcd for $C_{21}H_{30}ClO_2Si$ *ie* $[M+H]^+$ 377.1704. Found 377.1710. The diastereoselectivity was 1.0:10 determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 11.8 min (minor diastereomer), t_r 12.8 min (major diastereomer).

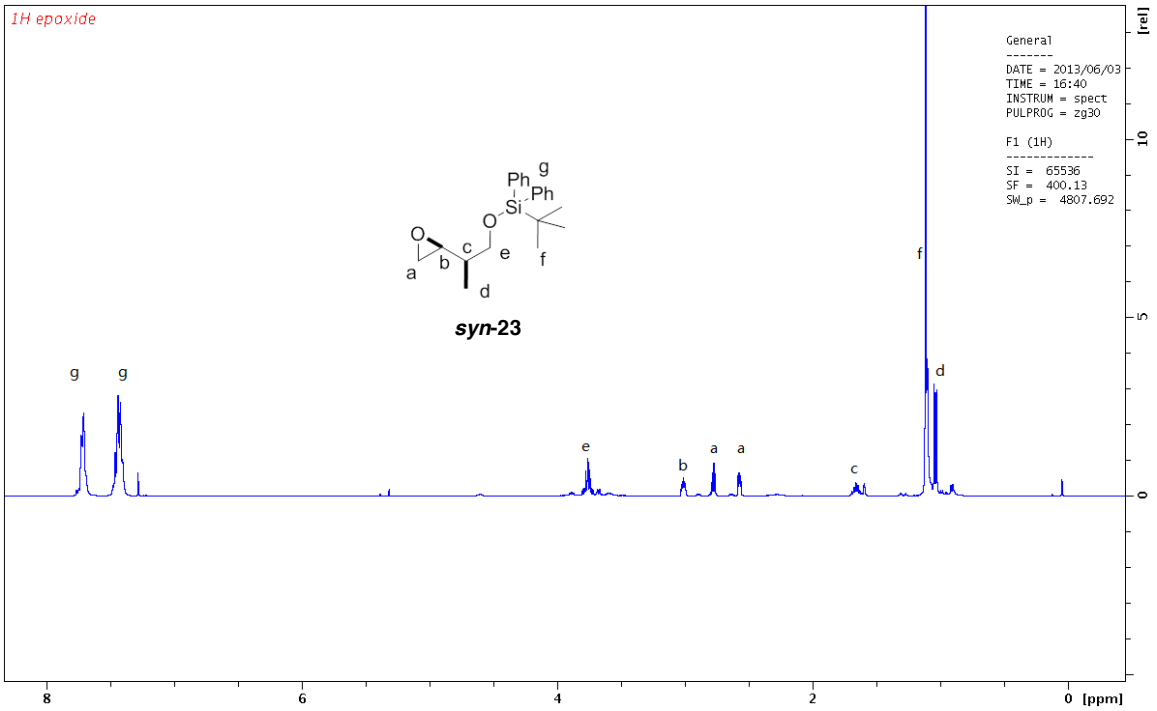
The product was then converted to the epoxide according to the typical procedure for preparation epoxides. Purification by flash chromatography afforded (2*S*,3*R*)-4-*tert*-butyldiphenylsilyloxy-1,3-epoxy-3-methylbutane (*syn*-**23**) as a colorless oil (61.3 mg, 90 % isolated yield). The relative stereochemistry was determined by comparing with a known epoxide, which was reported previously.[153] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.66 (4H, m), 7.48 – 7.38 (6H, m), 3.75 (2H, qd, *J* = 9.9, 5.1 Hz), 3.02 – 2.99 (1H, m), 2.81 – 2.75 (1H, m), 2.57 (1H, dd, *J* = 5.0, 2.8 Hz), 1.68 – 1.60 (1H, m), 1.10 (9H, s), 1.03 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.8, 129.6, 127.6, 66.2, 54.0, 45.6, 38.5, 26.9, 19.3, 12.6. IR (CH_2Cl_2) n (cm^{-1}) 3071, 2928, 2859, 1470, 1427, 1389, 1362, 1111, 933.6, 875.7, 821.7. HRMS (ESI): Exact mass calcd for $C_{21}H_{28}O_2SiLi$ *ie* $[M+Li]^+$ 347.2019. Found 347.2003.

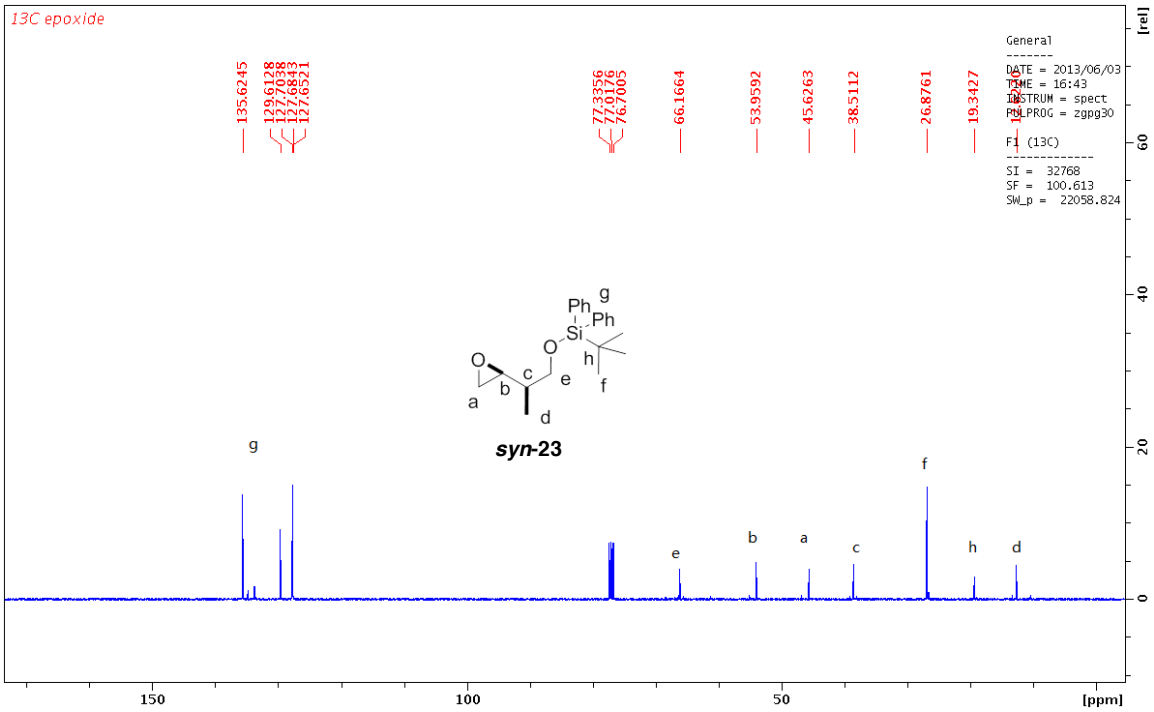
Relative stereochemistry determination of **20**: the ^{1}H NMR data of *syn*-**23** matched with reported data[153] and differs from that of *anti*-**23**. Therefore, the relative stereochemistry assignment was confirmed.



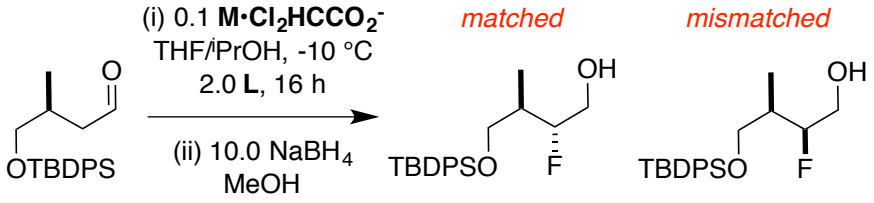



HSQC
Ph
g
Ph
Si
O
Cl
h
a
c
e
f
b
OH
d
anti-20
General
DATE = 2013/05/29
TIME = 18:51
INSTRUM = spect
PULPROG = hsqcetgpsi
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 5319.149
F1 (13C)
SI = 1024
SF = 100.613
SW_p = 16666.667
F1 [ppm]
40
60
80
100
120
140
8
6
4
2
F2 [ppm]


1H epoxide
Ph
g
Ph
Si
O
O
a
b
c
e
f
d
syn-23
General
DATE = 2013/06/03
TIME = 16:40
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 400.13
SW_p = 4807.692
[rel]
10
5
0
g
g
e
b
a
a
c
f
d
8
6
4
2
0 [ppm]



I. Typical Procedure for α-Fluorination of the Aldehyde:



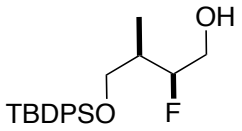
19

anti-**21**
(*R*)-M·Cl$_2$HCCO$_2^-$
85 %
syn:anti
1.0:58

syn-**21**
(*S*)-M·Cl$_2$HCCO$_2^-$
90 %
syn:anti
22:1.0

A modification of reported procedure[148] was used. 5-Benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (38 mg, 0.1 mmol) and *N*-fluorobenzenesulfonimide (315 mg, 1.0 mmol) was dissolved in THF (4.5 mL) and ^{i}PrOH (0.5 mL). The mixture was cooled to -10 °C prior to addition of the aldehyde (170 mg, 0.5 mmol). The resulting mixture was stirred at -10 °C for 16 h and was then warmed to 0 °C. To the mixture at 0 °C was added 1 mL MeOH and $NaBH_4$ (200 mg, 5

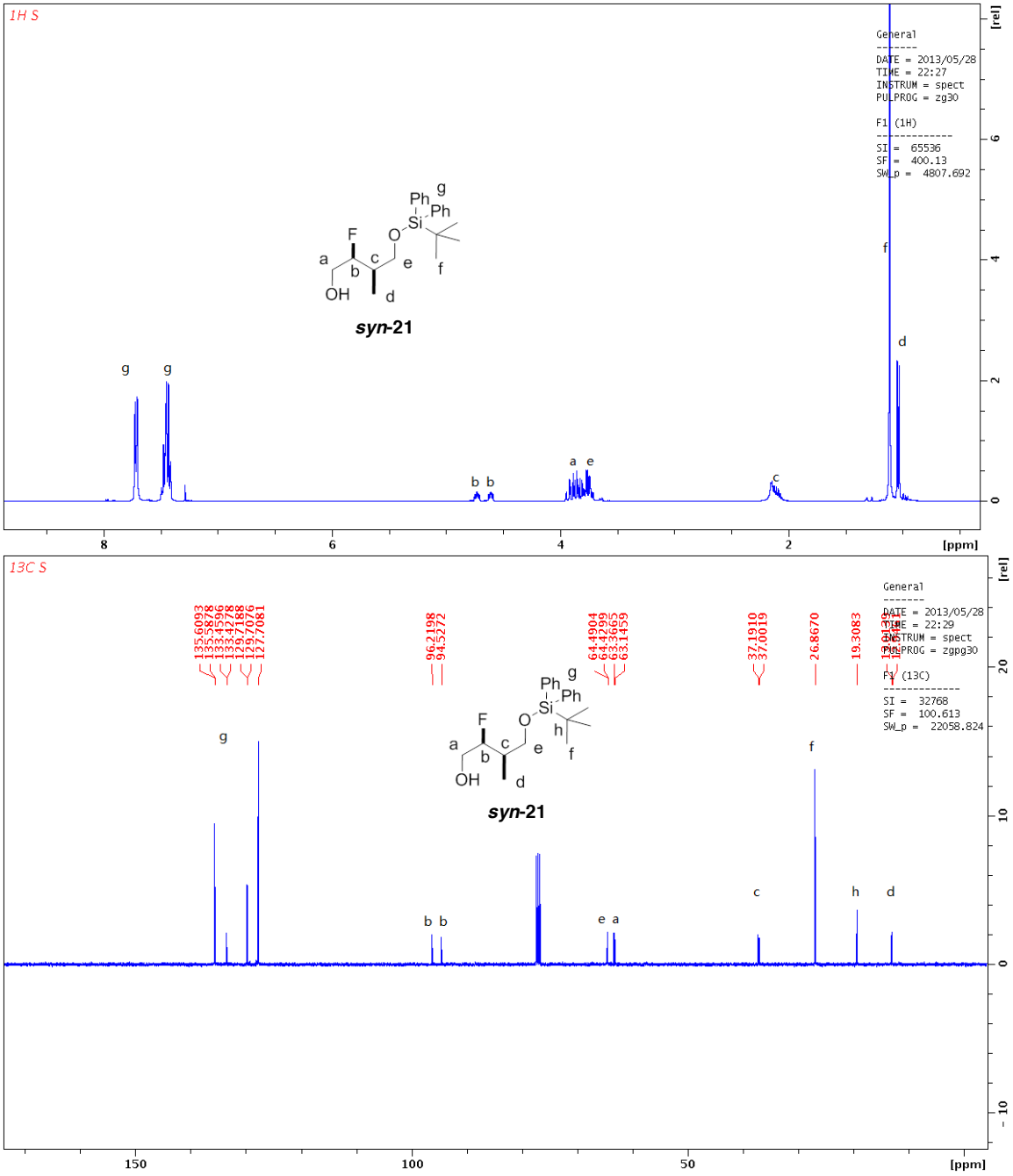
mmol). After stirring at 0 °C for 5 minutes, the reaction was quenched by 1 M $KHSO_4$. The mixture was diluted with water and the aqueous solution was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was redissolved in dichloromethane and the solid was filtered off on a small silica pad. The mixture was concentrated again *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 5 % ~ 10 % EtOAc/hexanes gave the desired alcohol as colorless oil.

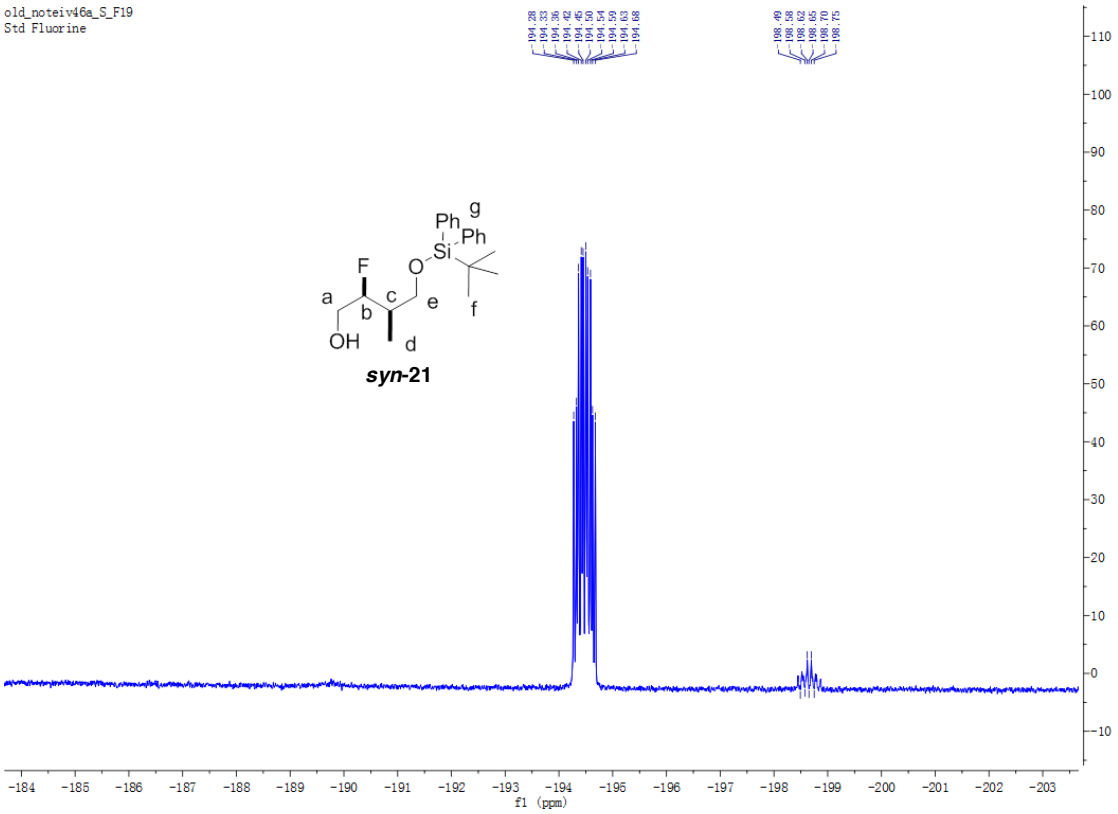


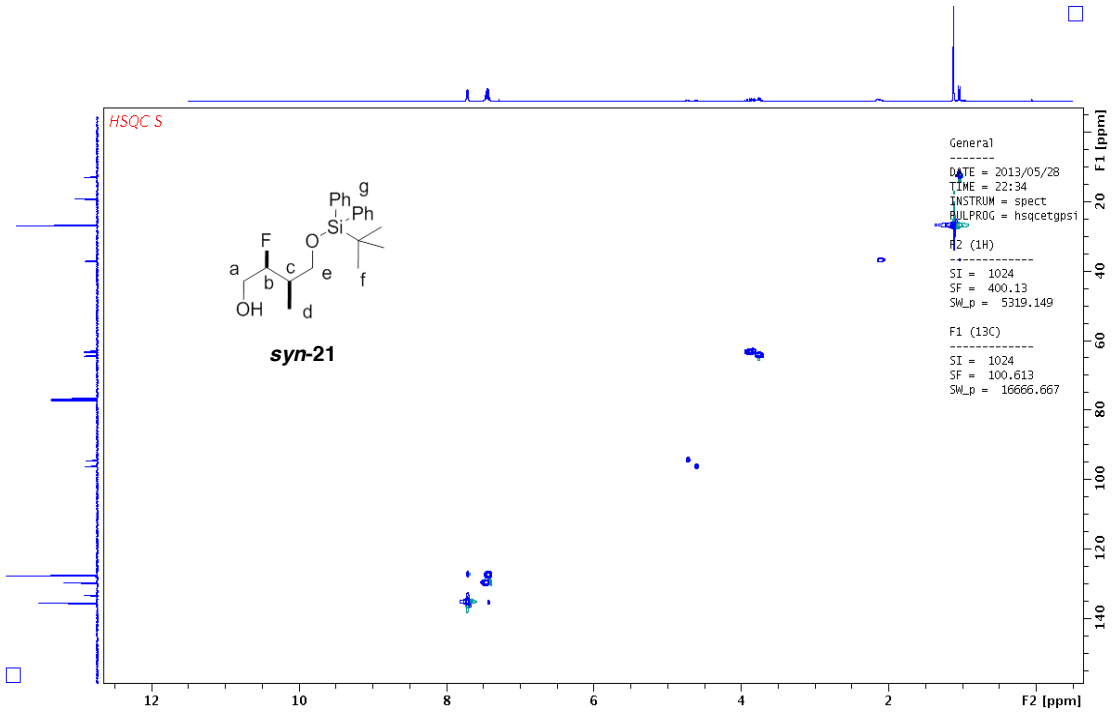
syn-**21**

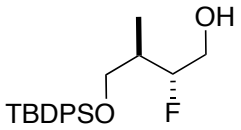
(2*S*,3*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-fluoro-3-methylbutan-1-ol (*syn*-21);

The compound was prepared according to the typical α-fluorination procedure catalysed by (*S*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt. Purification by flash chromatography afforded *syn*-**21** as a colorless oil (162 mg, 90 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.69 (4H, m), 7.51 – 7.39 (6H, m), 4.75 – 4.59 (1H, m), 3.96 – 3.68 (4H, m), 2.22 – 2.01 (2H, m), 1.11 (9H, s), 1.04 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d, J = 2.3 Hz), 133.5 (d, J = 3.1 Hz), 129.7 (d, J = 1.3 Hz), 127.7 (s), 95.4 (d, J = 170.3 Hz), 64.5 (d, J = 6.1 Hz), 63.3 (d, J = 22.2 Hz), 37.1 (d, J = 18.9 Hz), 26.9 (s), 19.3 (s), 13.0 (d, J = 6.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -194.48 (dtd, J = 40.0, 25.3, 14.5 Hz). IR (CH_2Cl_2) n (cm^{-1}) 3364, 3071, 2928, 2855, 2361, 1470, 1427, 1393, 1362, 1111, 1049. HRMS (ESI): Exact mass calcd for $C_{21}H_{30}FO_2Si$ *ie* $[M+H]^+$ 361.1999. Found 361.2021. The diastereoselectivity was 22:1.0 determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 16.05 min (major diastereomer), t_r 23.68 min (minor diastereomer).


1H S
General
DATE = 2013/05/28
TIME = 22:27
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 400.13
SW_p = 4807.692
[rel]
[ppm]
syn-21
13C S
General
DATE = 2013/05/28
TIME = 22:29
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
135.6093
133.4278
133.3596
133.4278
129.7188
129.7076
127.7081
96.2198
94.5272
64.4904
64.4269
63.4655
63.1459
37.1910
37.0019
26.8670
19.3083
[rel]
[ppm]
syn-21


old_noteiv46a_S_F19
Std Fluorine
194.28
194.33
194.36
194.42
194.45
194.50
194.54
194.59
194.63
194.68
198.49
198.58
198.62
198.65
198.70
198.75
Ph
Ph
g
Si
O
F
a
b
c
d
e
f
OH
syn-21
f1 (ppm)


HSQC S
Ph
Ph
g
Si
O
F
a
b
c
d
e
f
OH
syn-21
General
DATE = 2013/05/28
TIME = 22:34
INSTRUM = spect
PULPROG = hsqcetgpsi
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 5319.149
F1 (13C)
SI = 1024
SF = 100.613
SW_p = 16666.667
F2 [ppm]
F1 [ppm]

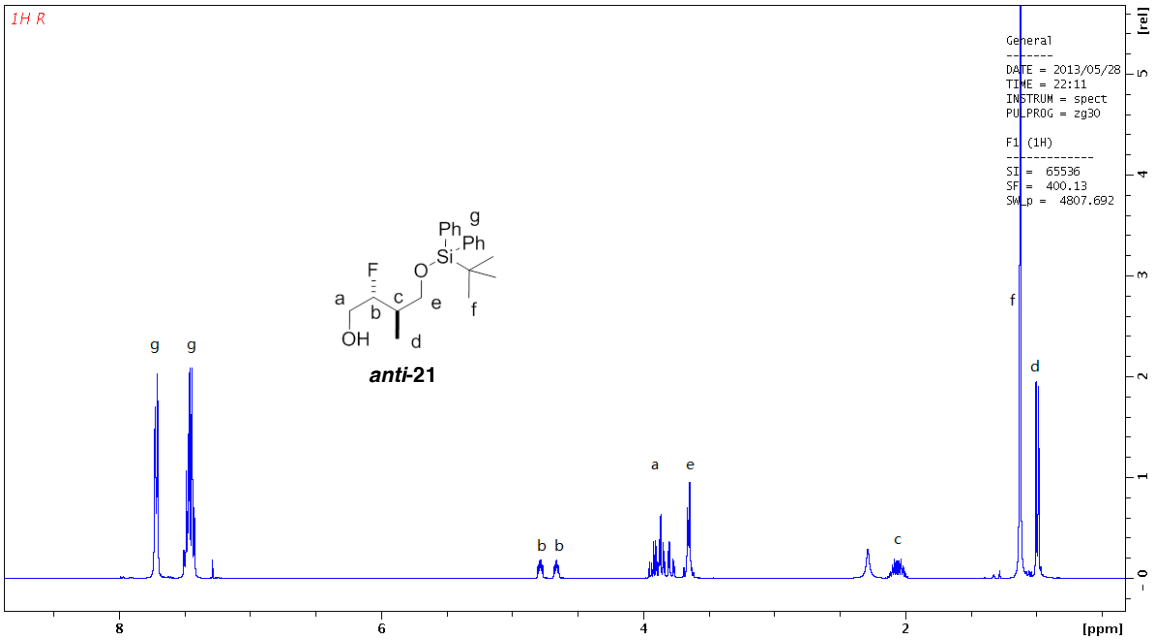


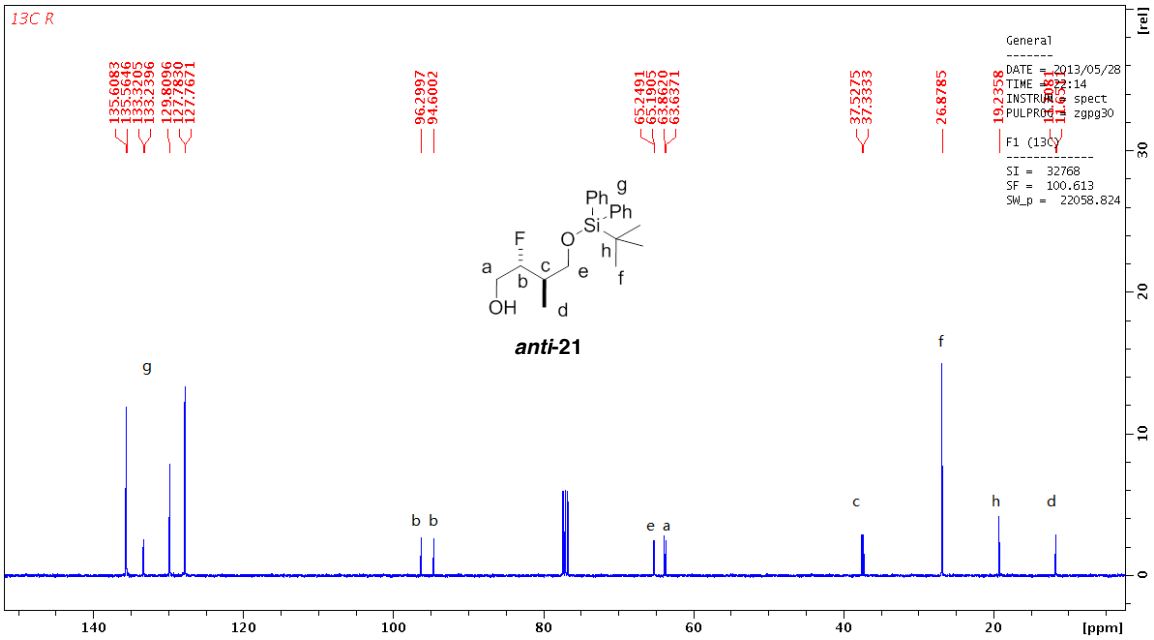
anti-**21**

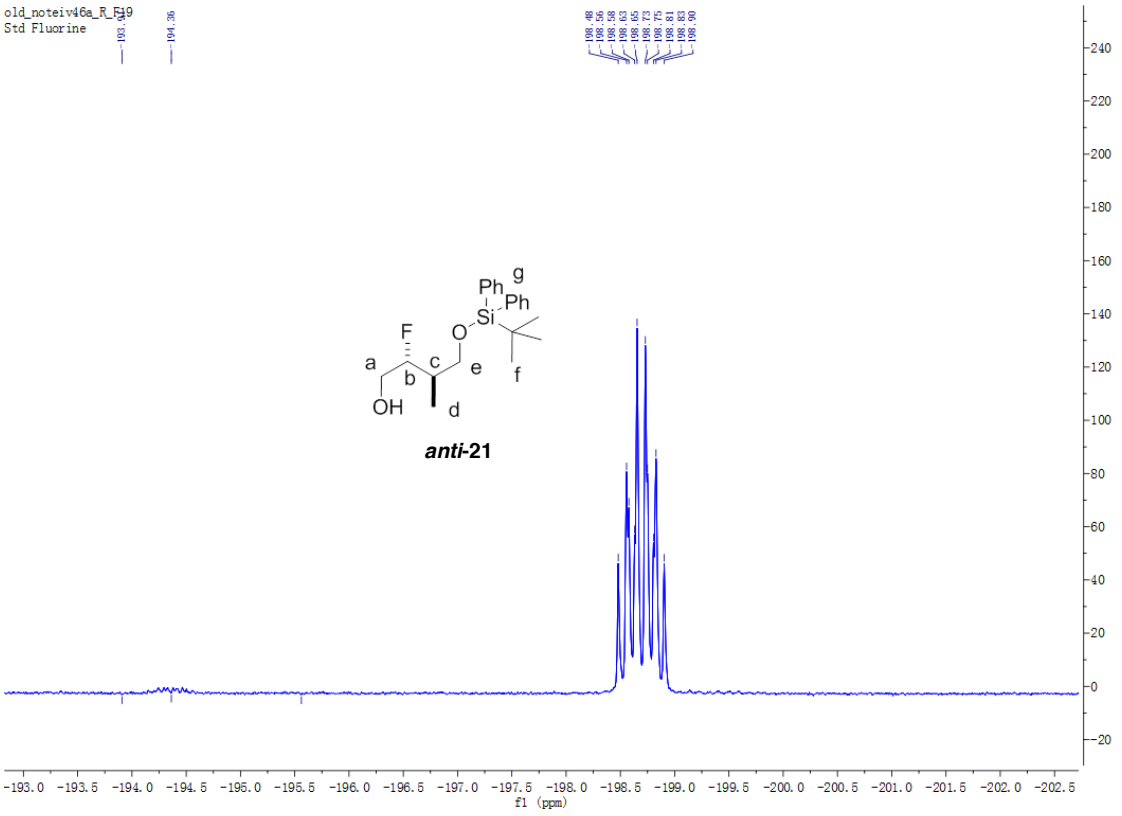
(2*R*,3*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-fluoro-3-methylbutan-1-ol (*anti*-21);

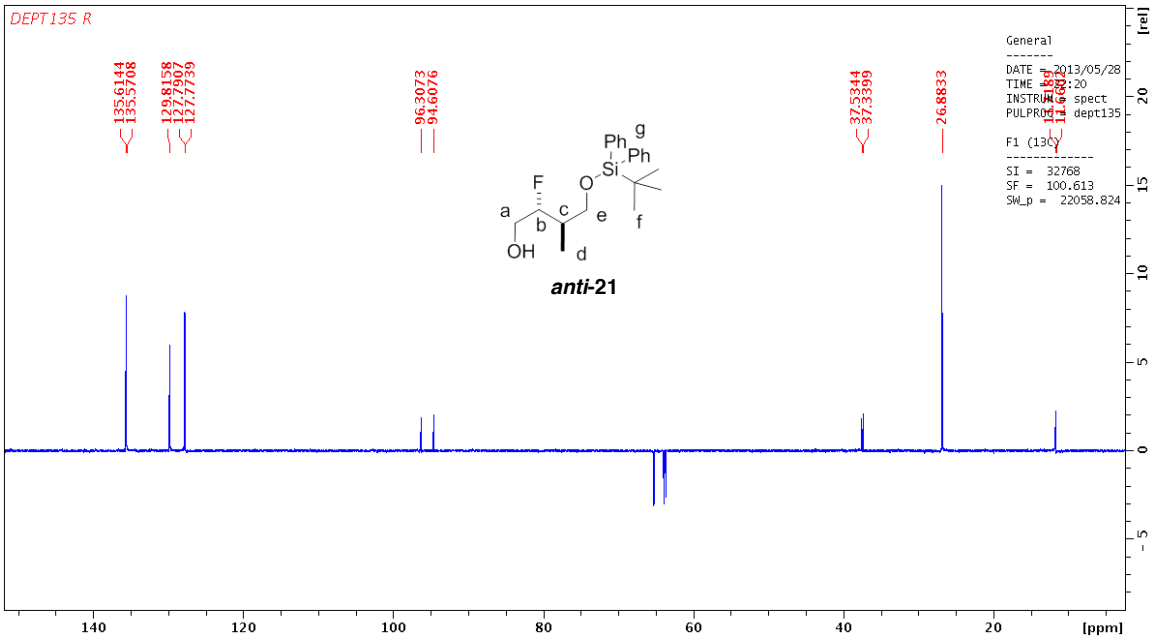
The compound was prepared according to the typical α-fluorination procedure catalysed by (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt. Purification by flash chromatography afforded *anti*-**21** as a colorless oil (153 mg, 85 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (4H, m), 7.51 – 7.41 (6H, m), 4.82 – 4.63 (1H, m), 3.97 – 3.75 (2H, m), 3.67 – 3.64 (2H, m), 2.28 (1H, br), 2.11– 2.00 (1H, m), 1.12 (9H, s), 0.99 (3H, dd, *J* = 7.0, 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d, *J* = 4.5 Hz), 133.3 (d, *J* = 8.2 Hz), 129.8 (s), 127.8 (d, *J* = 1.6 Hz), 95.4 (d, *J* = 171.0 Hz), 65.2 (d, *J* = 6.0 Hz), 63.7 (d, *J* = 22.6 Hz), 37.4 (d, *J* = 19.6 Hz), 26.9 (s), 11.7 (d, *J* = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -198.46 – -198.93 (m). IR (CH_2Cl_2) n (cm^{-1}) 3356, 3071, 2932, 2859, 2361, 1470, 1427, 1389, 1362, 1111, 1034. HRMS (ESI): Exact mass calcd for $C_{21}H_{30}FO_2Si$ *ie* $[M+H]^+$ 361.1999. Found 361.2035. The diastereoselectivity was 1.0:58, determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 16.05 min (minor diastereomer), t_r 23.68 min (major diastereomer).

Relative stereochemistry determination of **21**: since both catalyst and reaction condition are identical to what has been reported, and the reaction is catalyst controlled; the stereochemistry was assigned according to MacMillan's fluorinated product. The product cannot be easily converted to any known structure.

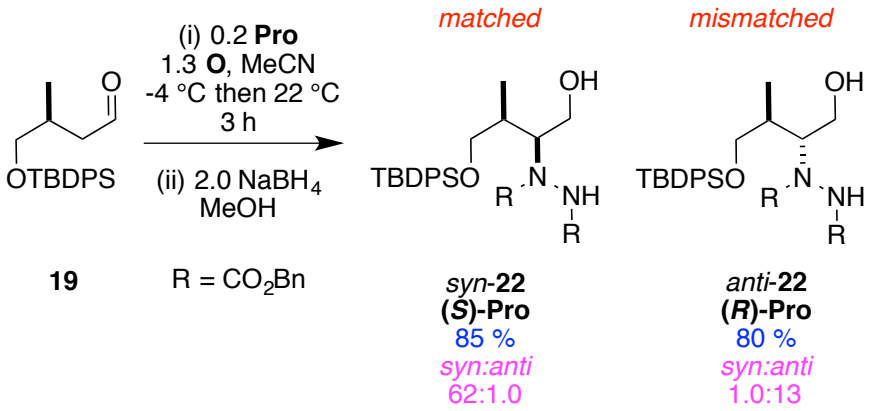

1H R
General
DATE = 2013/05/28
TIME = 22:11
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 400.13
SW_p = 4807.692
anti-21
[ppm]
[rel]


13C R
General
DATE = 2013/05/28
TIME = 22:14
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
anti-21
[ppm]
[rel]

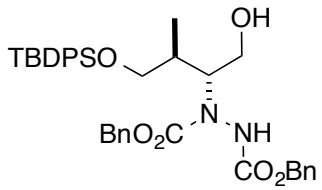

old_noteiv46a_R_F19
Std Fluorine
anti-21
f1 (ppm)


DEPT135 R
anti-21
[ppm]
[rel]

J. Typical Procedure for the α-Amination of the Aldehyde:



A modification of reported procedure[269] was used. Dibenzyl azodicarboxylate (90 %, 1.29 g, 3.9 mmol) and proline (70 mg, 0.6 mmol) in MeCN (10 mL) were cooled down to -3 °C. The aldehyde (1.02 g 3.0 mmol) was then added and the mixture was stirred at -3 °C for 2 h. The reaction was gradually warmed to 20 °C within *ca.* 1 h. The mixture was then cooled to 0 °C, treated with MeOH (3 mL) and $NaBH_4$ (240 mg, 6 mmol) and was stirred for 5 min at 0 °C. The reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 15 % EtOAc/hexanes gave the desired alcohol as white foamy solid.

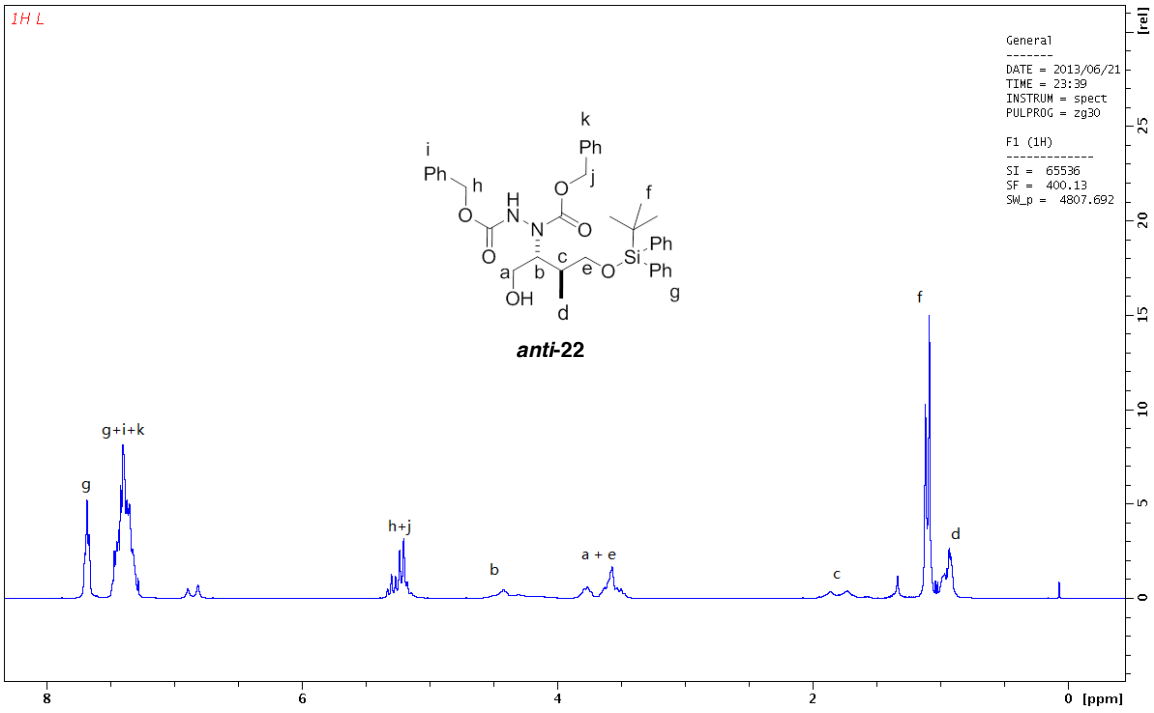


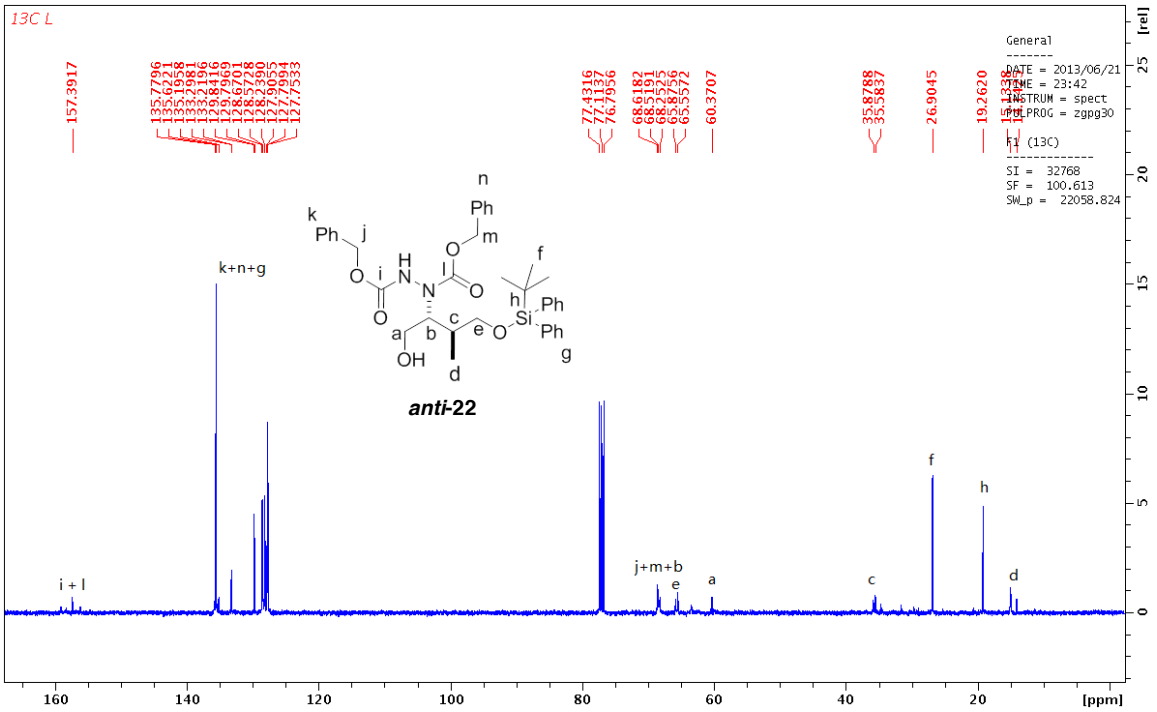
anti-**22**

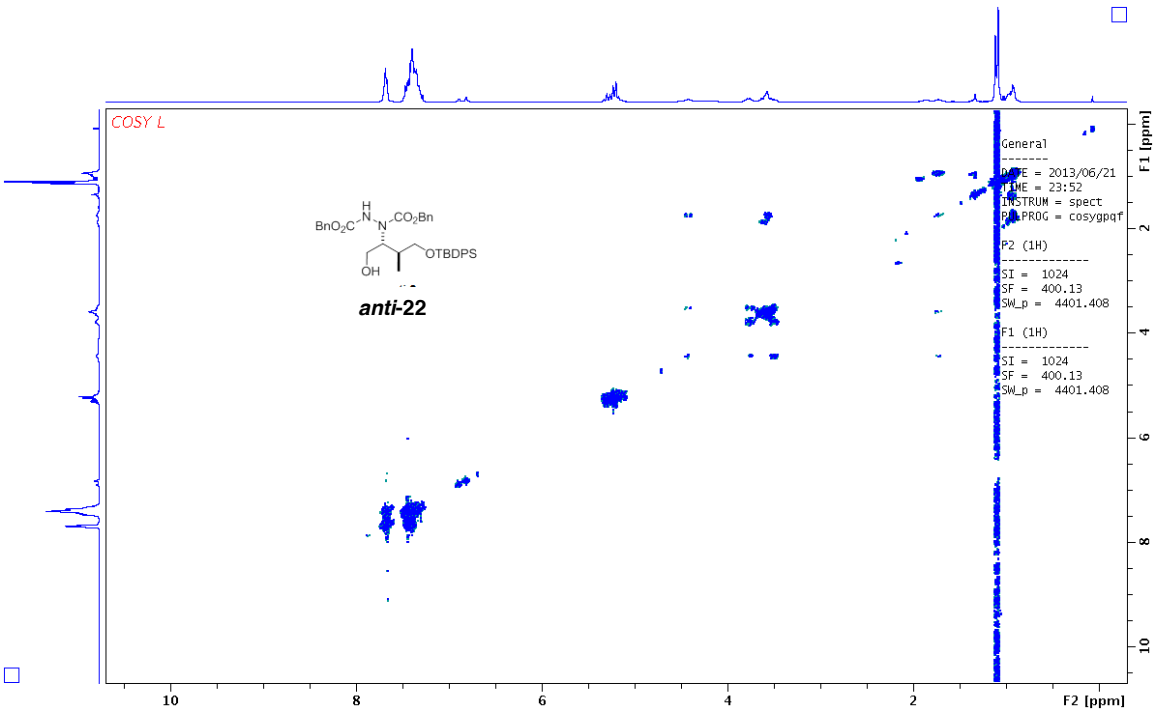
Dibenzyl 1-((2*R*,3*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)hydrazine-1,2-dicarboxylate (*anti*-22);

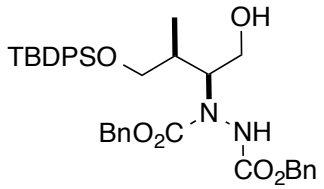
The compound was prepared according to the typical α-amination procedure catalysed by (*R*)-Proline. Purification by flash chromatography afforded *anti*-**22** as a

white foamy solid (1.54 g, 80 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.67 (4H, m), 7.50 – 7.27 (16H, m), 6.85 (1H, d, J = 31.1 Hz), 5.37 – 5.10 (4H, m), 4.45 – 4.12 (2H, m), 3.80 – 3.41 (4H, m), 1.95 – 1.66 (1H, m), 1.12 – 1.09 (9H, m), 0.99 – 0.88 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.4, 135.6, 133.3, 133.2, 129.6, 129.8, 128.7, 128.6, 128.2, 127.9, 127.8, 127.7, 68.6, 65.9, 65.6, 60.4, 35.6, 26.9, 19.3, 15.1. IR (CH_2Cl_2) n (cm^{-1}) 3356, 3032, 2928, 1717, 1454, 1408, 1265, 1227, 1111, 1057. HRMS (ESI): Exact mass calcd for $C_{37}H_{45}N_2O_6Si$ *ie* $[M+H]^+$ 641.3047. Found 641.3078. The diastereoselectivity was 1.0:13, determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 93:7, 1 mL/min, 25 °C), t_r 10.3 min (minor diastereomer), t_r 14.4 min (major diastereomer).




13C L
157.3917
135.7796
135.6711
135.1658
133.2681
133.2196
129.8416
129.7969
128.7701
128.5728
128.2390
127.9055
127.7994
127.7333
77.4316
77.1137
76.7956
68.6182
68.3191
68.2525
65.5526
65.3572
60.3707
35.8788
35.5837
26.9045
19.2620
15.1338
14.1024
General
DATE = 2013/06/21
TIME = 23:42
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
k+n+g
i + l
j+m+b
e
a
c
f
h
d
anti-22
[rel]
[ppm]

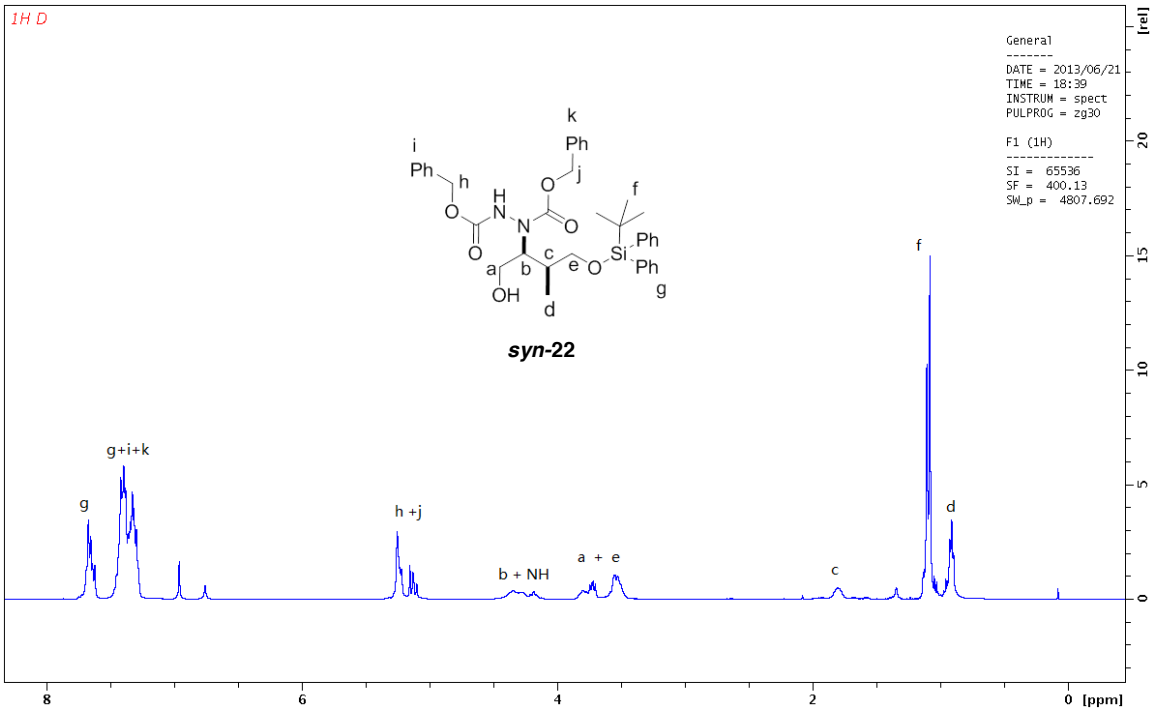

COSY L
anti-22
General
DATE = 2013/06/21
TIME = 23:52
INSTRUM = spect
PULPROG = cosygpqf
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 4401.408
F1 (1H)
SI = 1024
SF = 400.13
SW_p = 4401.408
F1 [ppm]
F2 [ppm]

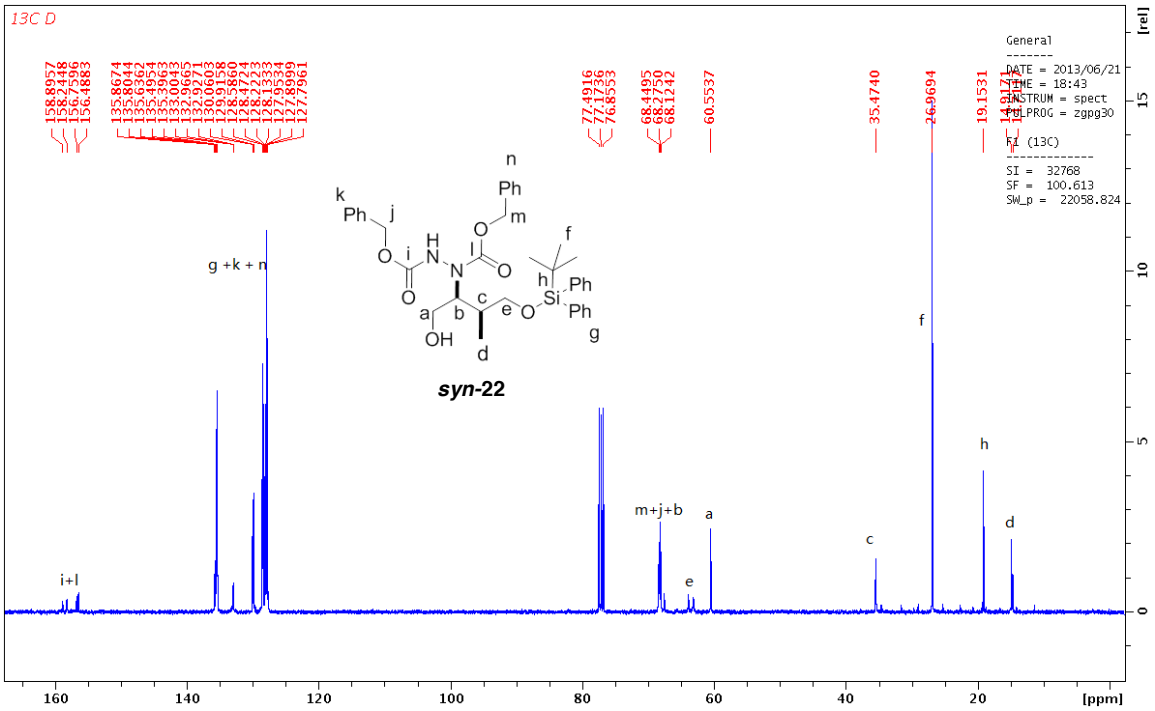


syn-**22**

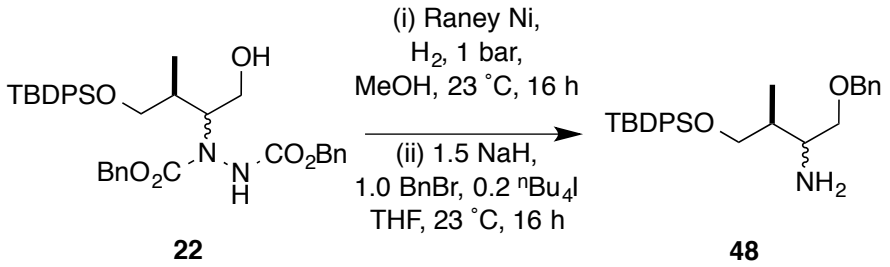
Dibenzyl 1-((2*S*,3*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)hydrazine-1,2-dicarboxylate (*syn*-22);

The compound was prepared according to the typical α-amidation procedure catalysed by (*S*)-Proline. Purification by flash chromatography afforded *syn*-**22** as a white foamy solid (1.63 g, 85 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (4H, m, *J* = 13.5, 6.6 Hz), 7.50 – 7.24 (16H, m), 6.96 (1H, s), 5.30 – 5.22 (3H, m), 5.13 (1H, dd, *J* = 12.1, 9.6 Hz), 4.36 – 4.16 (2H, m), 3.86 – 3.70 (2H, m), 3.59 – 3.44 (2H, m), 1.80 (1H, br), 1.11 – 1.08 (9H, m), 0.93 – 0.90 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (d, *J* = 65.9 Hz), 156.6 (d, *J* = 27.3 Hz), 135.8, 135.6, 135.5, 135.4, 133.0, 130.1, 129.9, 128.6, 128.5, 128.1, 127.9, 127.8, 68.3, 64.0, 63.2, 60.6, 35.5, 27.0, 19.2, 14.9. IR (CH_2Cl_2) n (cm^{-1}) 3356, 3032, 2959, 1724, 1470, 1408, 1261, 1223, 1111, 1053. HRMS (ESI): Exact mass calcd for $C_{37}H_{45}N_2O_6Si$ *ie* $[M+H]^+$ 641.3047. Found 641.3063. The diastereoselectivity was 62:1.0, determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 93:7, 1 mL/min, 25 °C), t_r 10.2 min (minor diastereomer), t_r 14.3 min (major diastereomer).


1H D
General
DATE = 2013/06/21
TIME = 18:39
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 400.13
SW_p = 4807.692
syn-22
g
g+i+k
h +j
b + NH
a + e
c
f
d
[rel]
[ppm]

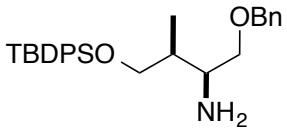

13C D
General
DATE = 2013/06/21
TIME = 18:43
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
syn-22
g +k + n
i+l
m+j+b
a
e
c
f
h
d
[rel]
[ppm]

K. Typical Procedure for the Hydrogenolysis and Benzylation of the Alcohol.



22 **48**

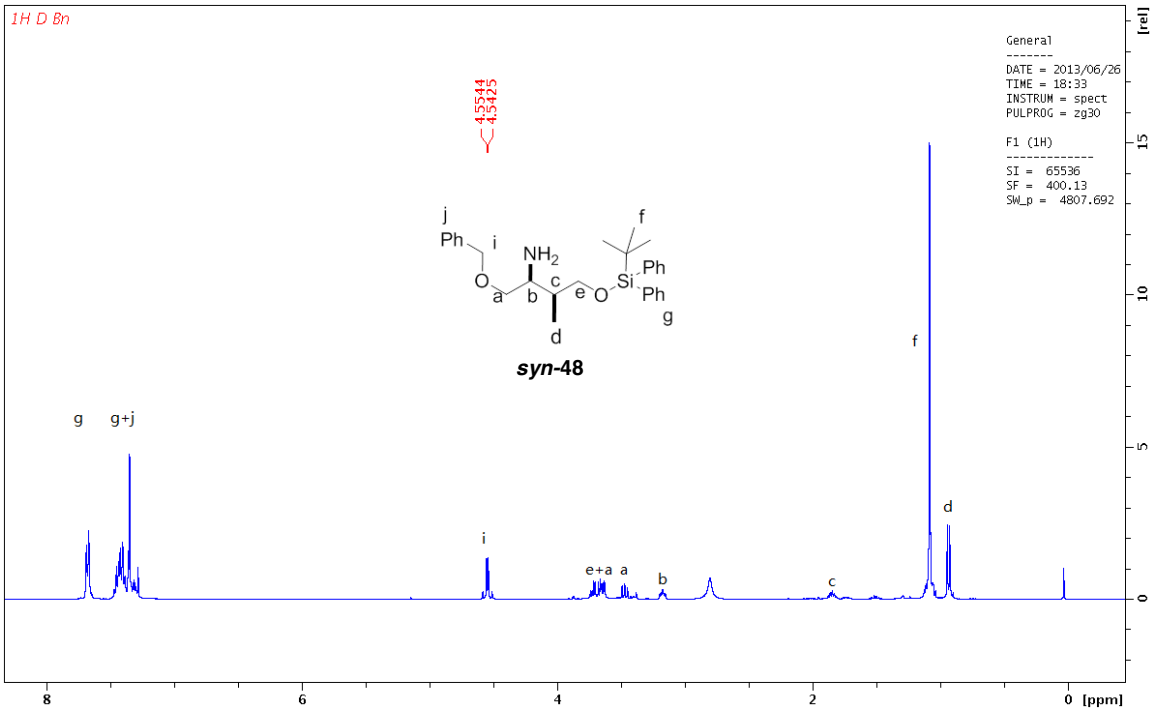
To Raney–Nickel (~0.3 g, prewashed with dry MeOH) in MeOH (1 mL), was added AcOH (0.3 mL) and a solution of 9 (0.1 mmol) in MeOH (1 mL). The solution was degassed and stirred under a slightly positive pressure of hydrogen (balloon) at 23 °C for 16 h. The reaction was then filtered through a short pad of Celite, and washed with CH_2Cl_2. The mixture was concentrated *in vacuo* and the residue was redissolved in CH_2Cl_2 and was neutralized by anhydrous Na_2CO_3. The solvent was removed by vacuum and the crude product was subjected to benzyl protection without further purification. Under Ar atmosphere, to a solution of the hydrogenated crude product (0.15 mmol) in anhydrous THF was added NaH (4.8 mg, 0.4 mmol). After stirring for 5 min, BnBr (19 mL, 0.15 mmol) and $^nBu_4NI$ (11.1 mg, 0.03 mmol) was added and the mixture was stirred at 23 °C for 16 h. The reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with EtOAc (three times). The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 1.0 % ~ 2.5 % MeOH/CH_2Cl_2 gave the desired product as a white foamy solid.

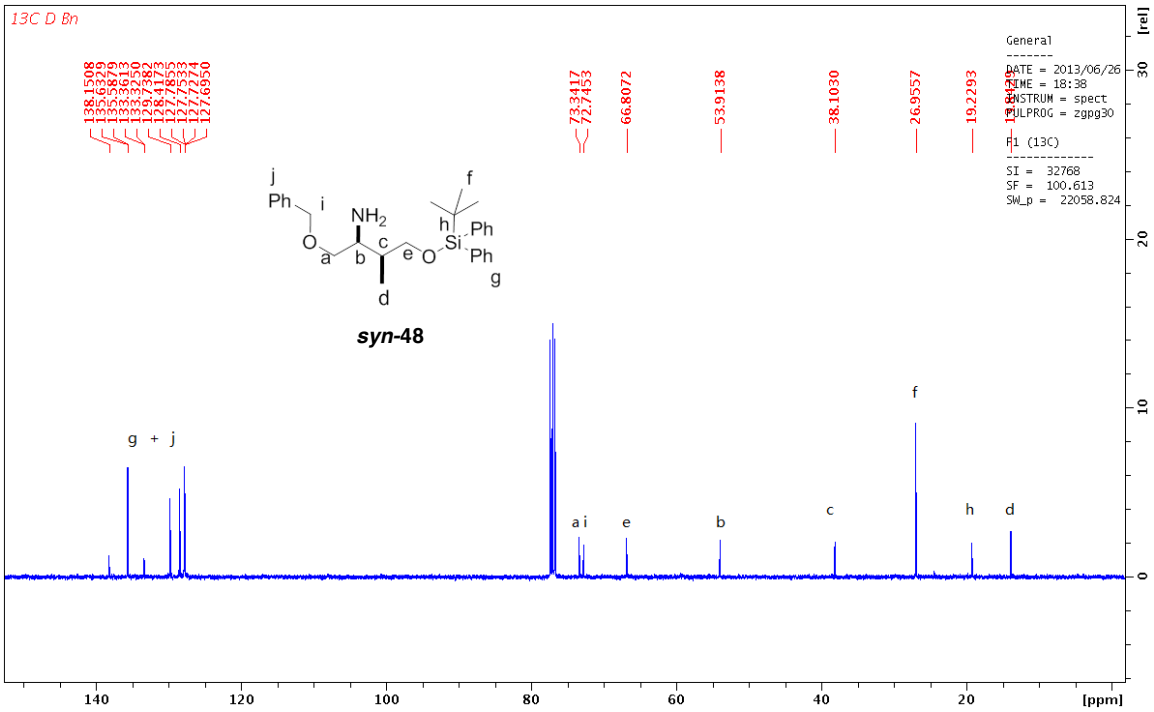


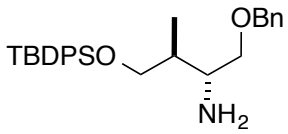
syn-**48**

(2*S*,3*S*)-1-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutan-2-amine (*syn*-48);

The compound was prepared according to the typical hydrogenolysis and benzylation procedure. Purification by flash chromatography afforded *syn*-**48** as a white foamy solid (22.2 mg, 50 % yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (4H, m), 7.48 – 7.28 (11H, m), 4.55 (2H, d, J = 4.8 Hz), 3.77 – 3.60 (3H, m), 3.47 (1H, dd, J = 9.3, 7.6 Hz), 3.18 (1H, td, J = 7.2, 3.4 Hz), 2.80 (2H, br), 1.90 – 1.79 (1H, m), 1.08 (9H, s), 0.94 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.6, 133.4, 133.3, 129.7, 128.4, 127.8, 127.7, 73.3, 72.8, 66.8, 53.9, 38.1, 27.0, 19.2, 13.9.





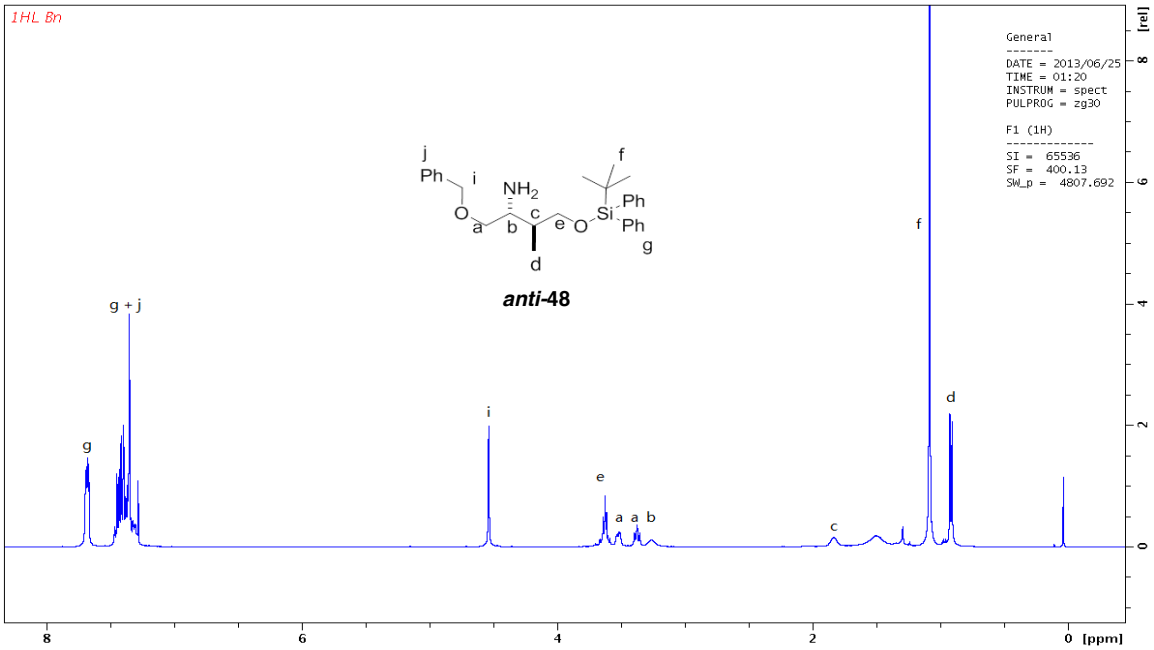


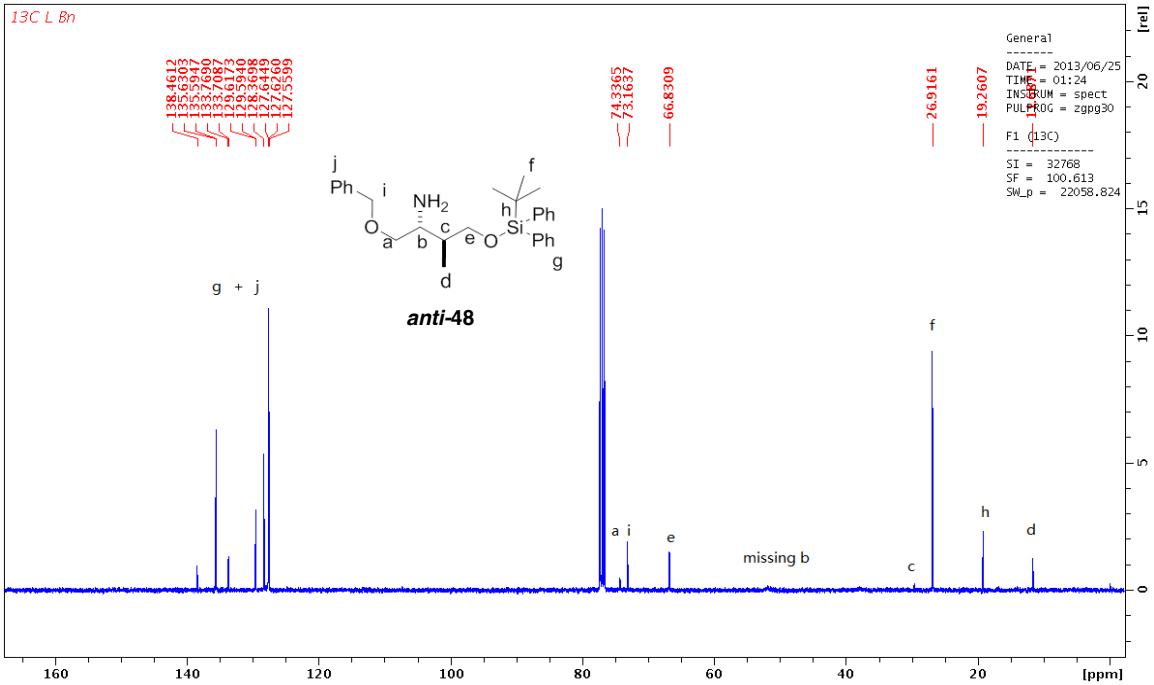
anti-**48**

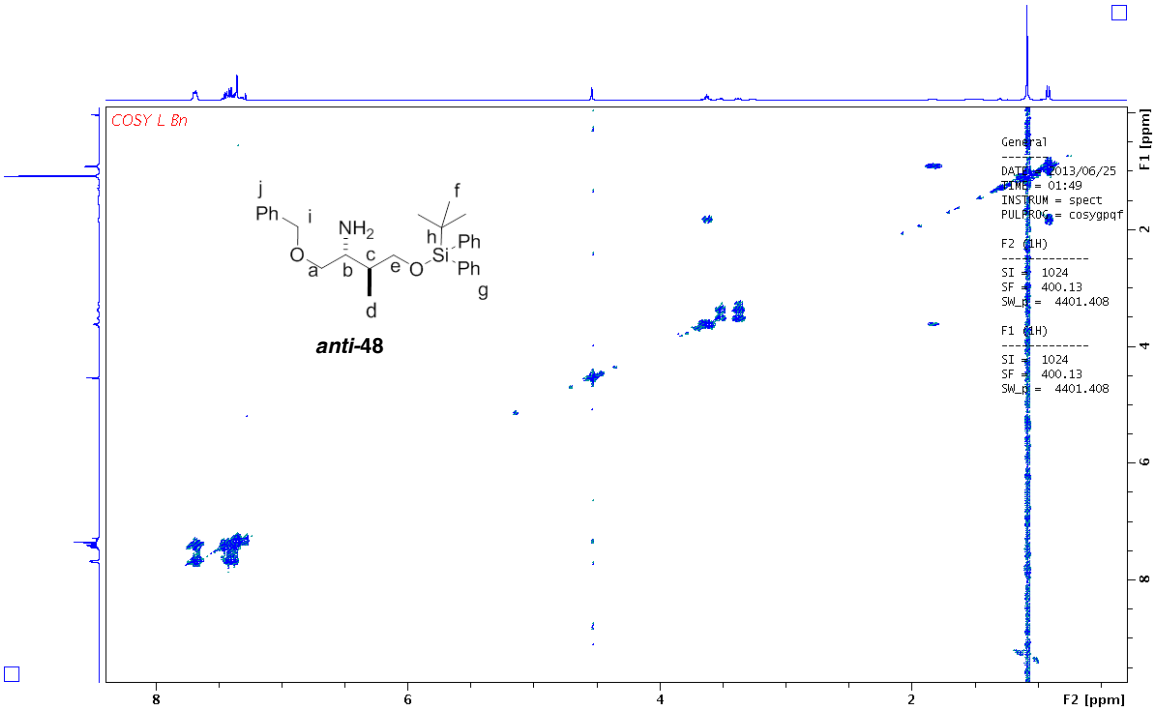
(2*R*,3*S*)-1-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutan-2-amine (*anti*-48);

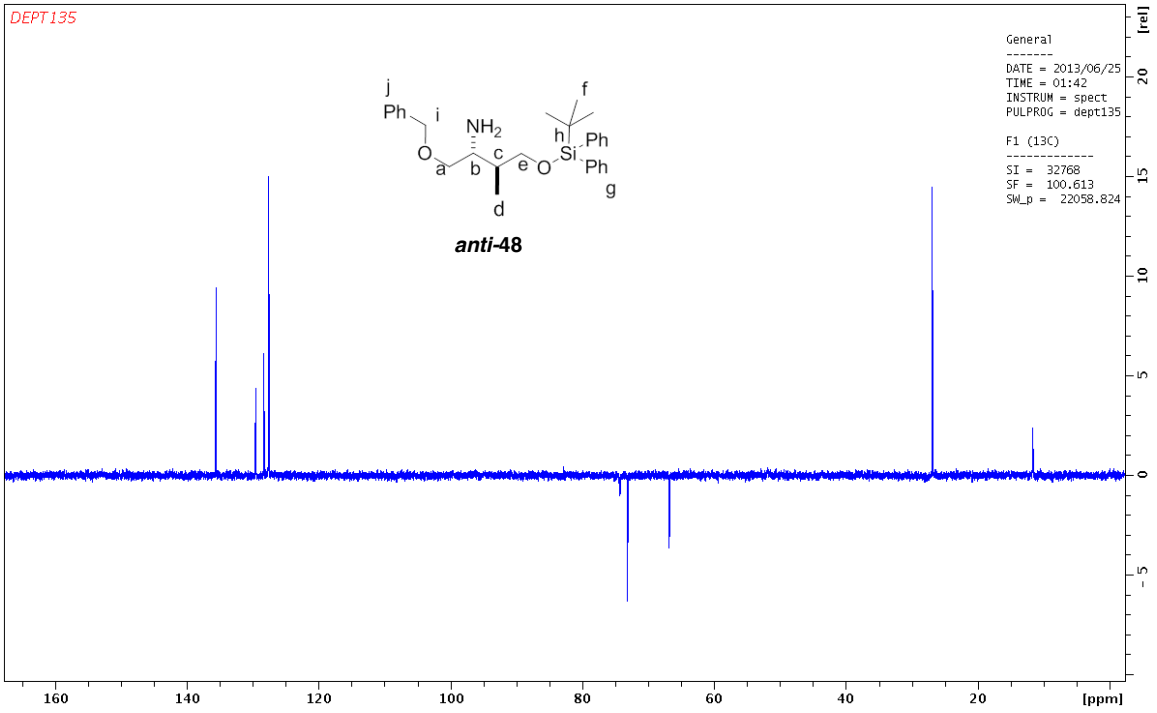
The compound was prepared according to the typical hydrogenolysis and benzylation procedure. Purification by flash chromatography afforded *anti*-**48** as a white foamy solid (22.3 mg, 50 % yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.67 (4H, m), 7.49 – 7.28 (11H, m), 4.54 (2H, s), 3.68 – 3.58 (2H, m), 3.56 – 3.49 (1H, m), 3.38 (1H, dd, J = 10.2, 6.5 Hz), 3.26 (1H, br), 1.83 (1H, br), 1.51 (2H, br), 1.08 (9H, s), 0.92 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 135.6, 133.8, 133.7, 129.6, 128.4, 127.7, 127.6, 74.3, 73.2, 66.8, 29.7, 26.9, 19.3, 11.7.

Relative stereochemistry determination of **22**: the ^{13}C NMR data of *syn*-**48** matched with reported data[270] and differ from that of *anti*-**48**. Therefore, the relative stereochemistry assignment was confirmed.

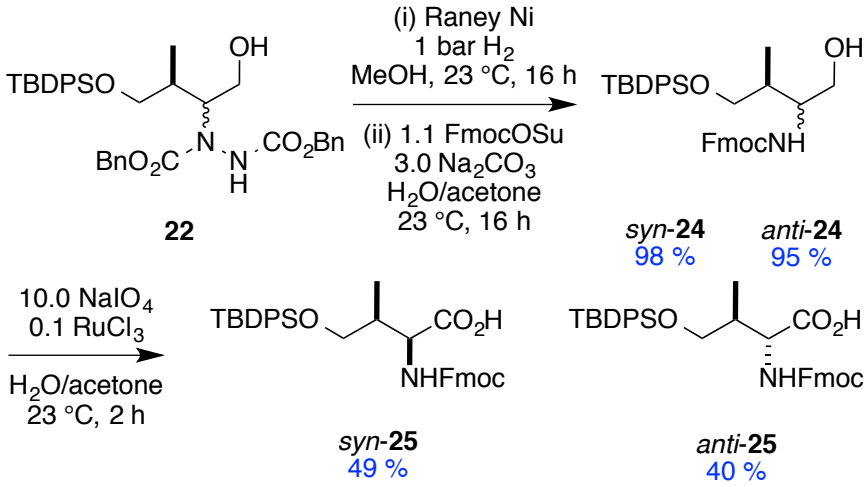





COSY L Bn
anti-48
F2 [ppm]
F1 [ppm]

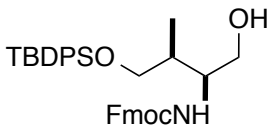

DEPT135
anti-48
[ppm]
[rel]

L. Typical Procedure for the Preparation of α-Amino Acid.



To Raney–Nickel (~1.5 g, prewashed with dry MeOH) in MeOH (10 mL), was added AcOH (3 mL) and a solution of **22** (2.25 mmol) in MeOH (10 mL). The solution was degassed and stirred under a slightly positive pressure of hydrogen (balloon) at 23 °C for 16 h. The reaction was then filtered through a short pad of Celite, and washed with CH_2Cl_2. The mixture was concentrated *in vacuo* and the residue was redissolved in CH_2Cl_2 and was neutralized by anhydrous Na_2CO_3. The solvent was removed by vacuum and the crude product was subjected to Fmoc-protection without further purification. To a solution of the above crude product in H_2O (10 mL) and acetone (10 mL) was added FmocOSu (830 mg, 2.5 mmol) and Na_2CO_3 (715 mg, 6.7 mmol). The reaction was stirred at 23 °C for 16 h. The mixture was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 10 % ~ 20 % EtOAc/hexanes gave **24** as a white foamy solid. To a solution of $RuCl_3$ (29 mg, 0.14 mmol) and $NaIO_4$ (2.95 g, 13.8 mmol) in water was added 12 (800 mg, 1.38 mmol). The mixture was stirred at 23 °C for 2 h, and then added MeOH (2 mL). The reaction was stirred until solid precipitation occurred. The solid was filtered on Celite and washed it with EtOAc. 1 M $KHSO_4$ (3 mL) was added to the filtrate. Then, the aqueous phase was extracted by EtOAc. The combined organic layers were dried with $MgSO_4$, and

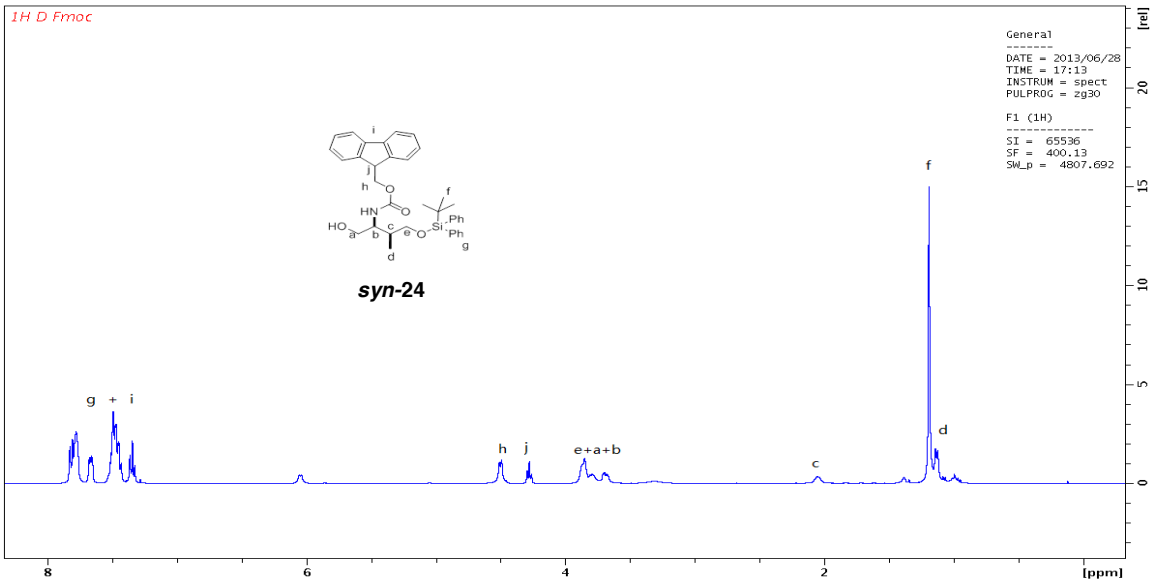
concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 15 % ~ 50 % EtOAc/hexanes gave the desired acid as a white foamy solid.

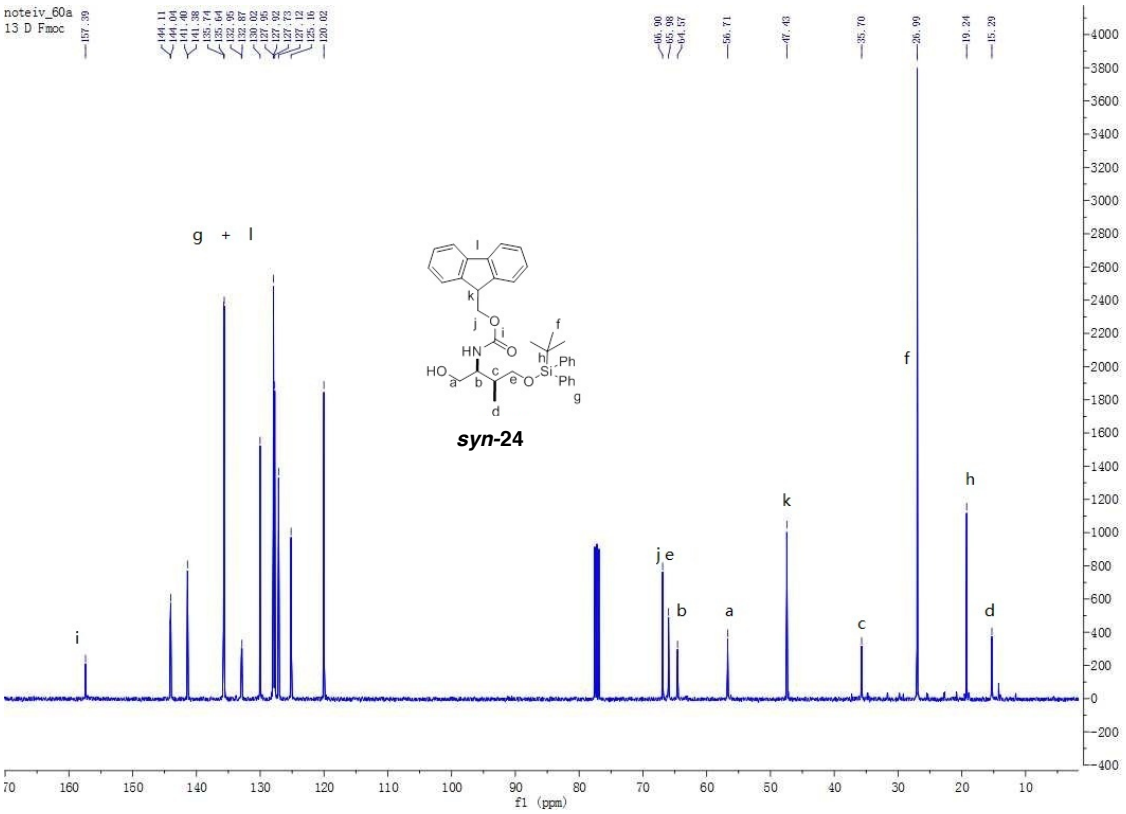


syn-**24**

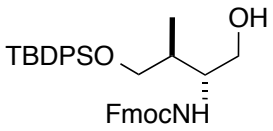
(9*H*-Fluoren-9-yl)methyl ((2*S*,3*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)carbamate (*syn*-24);

Purification by flash chromatography afforded *syn*-**24** as a white foamy solid (1.28 g, 98 % yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.74 (6H, m), 7.66 (2H, dd, *J* = 7.3, 3.6 Hz), 7.55 – 7.40 (8H, m), 7.34 (2H, t, *J* = 7.4 Hz), 6.05 (1H, d, *J* = 6.7 Hz), 4.50 (2H, d, *J* = 6.5 Hz), 4.28 (1H, t, *J* = 6.8 Hz), 3.93 – 3.74 (4H, m), 3.69 (1H, dd, *J* = 10.4, 4.5 Hz), 3.31 (1H, br), 2.05 (1H, br), 1.19 (9H, s), 1.13 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 144.1, 141.4, 135.7, 132.9, 130.0, 127.9, 127.7, 127.1, 125.2, 120.0, 66.9, 66.0, 64.6, 56.7, 47.4, 35.7, 27.0, 19.2, 15.3. IR (CH_2Cl_2) n (cm^{-1}) 3402, 3067, 2928, 1701, 1508, 1450, 1327, 1227, 1111, 1042. HRMS (ESI): Exact mass calcd for $C_{36}H_{42}NO_4Si$ *ie* $[M+H]^+$ 580.2883. Found 580.2874.





syn-**24**

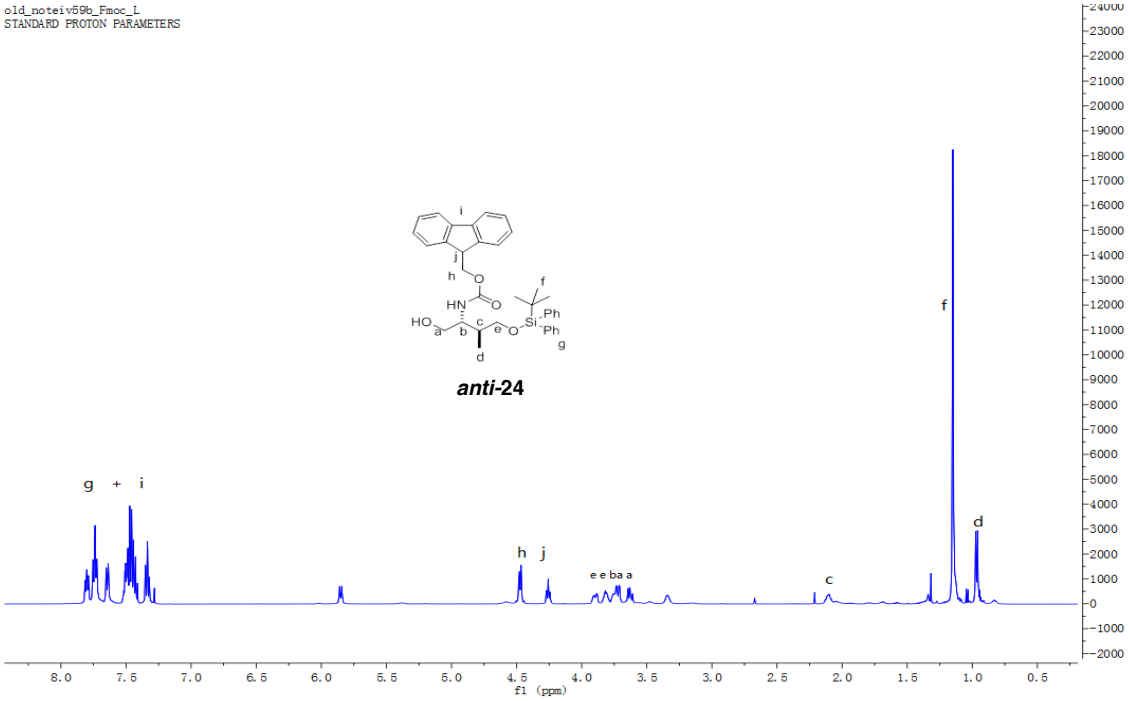


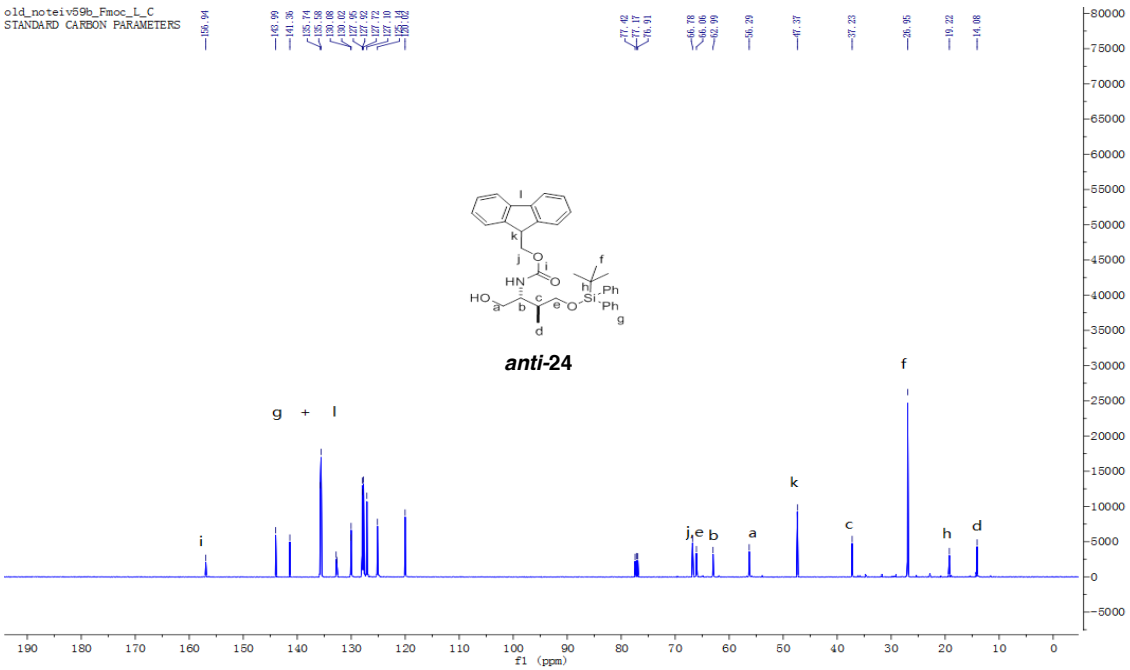
anti-**24**

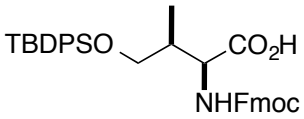
(9*H*-Fluoren-9-yl)methyl ((2*R*,3*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)carbamate (*anti*-24);

Purification by flash chromatography afforded *anti*-**24** as a white foamy solid (1.24 g, 95 % yield in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.77 (2H, m), 7.74 (4H, dd, *J* = 7.7, 6.7 Hz), 7.64 (2H, d, *J* = 7.4 Hz), 7.55 – 7.39 (8H, m), 7.33 (2H, td, *J* = 7.5, 1.0 Hz), 5.85 (1H, d, *J* = 8.3 Hz), 4.51 – 4.43 (2H, m), 4.26 (1H, t, *J* = 6.9 Hz), 3.90 (1H, dd, *J* = 11.2, 4.2 Hz), 3.83 – 3.80 (1H, m), 3.78 – 3.69 (2H, m), 3.63 (1H, dd, *J* = 10.7, 7.2 Hz), 3.34 (1H, br), 2.11 – 2.10 (1H, m), 1.15 (9H, s), 0.97 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 144.0, 141.4, 135.7, 132.8, 130.1, 127.9,

127.7, 127.1, 125.1, 120.0, 66.8, 66.1, 63.0, 56.3, 47.4, 37.2, 27.0, 19.2, 14.1. IR (CH_2Cl_2) n (cm^{-1}) 3368, 3067, 2928, 1701, 1512, 1450, 1242, 1111. HRMS (ESI): Exact mass calcd for $C_{36}H_{42}NO_4Si$ *ie* $[M+H]^+$ 580.2883. Found 580.2865.



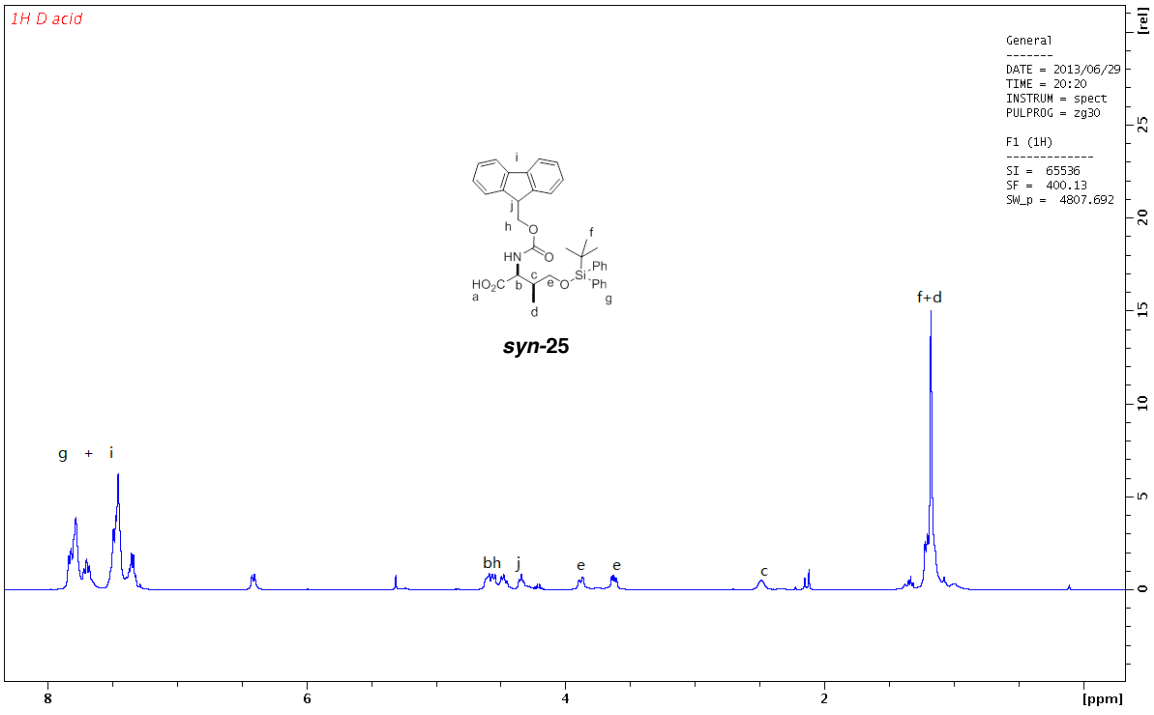


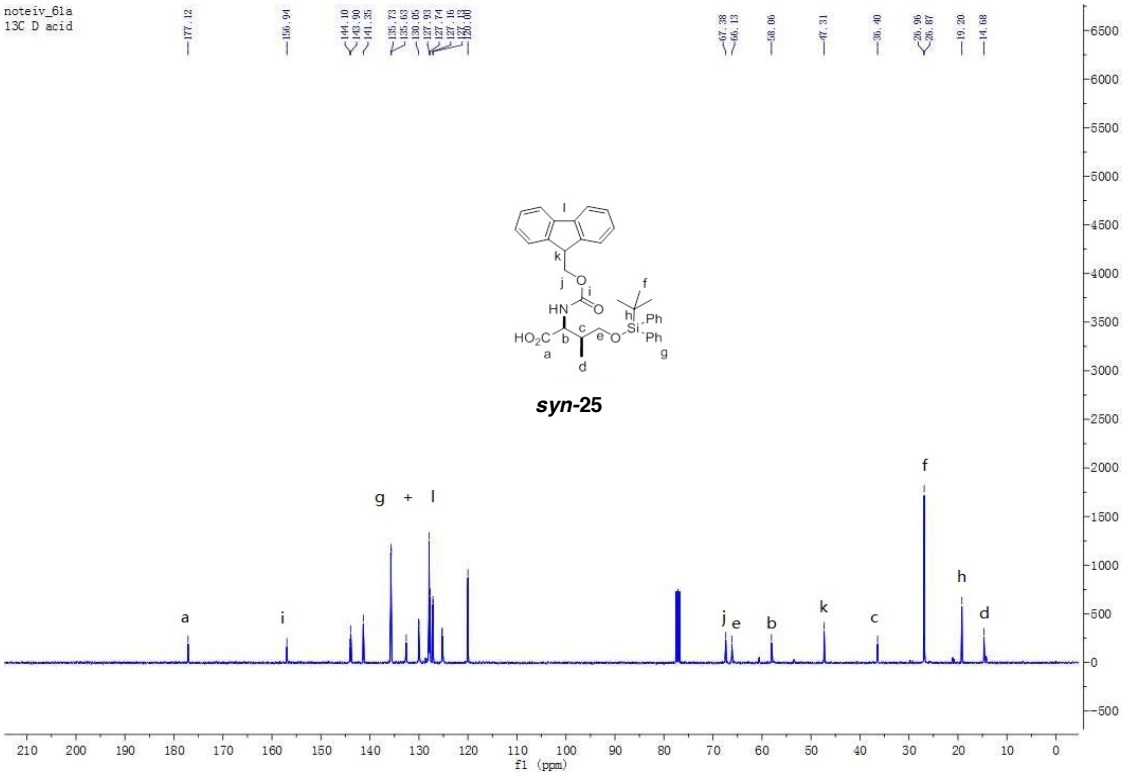


syn-**25**

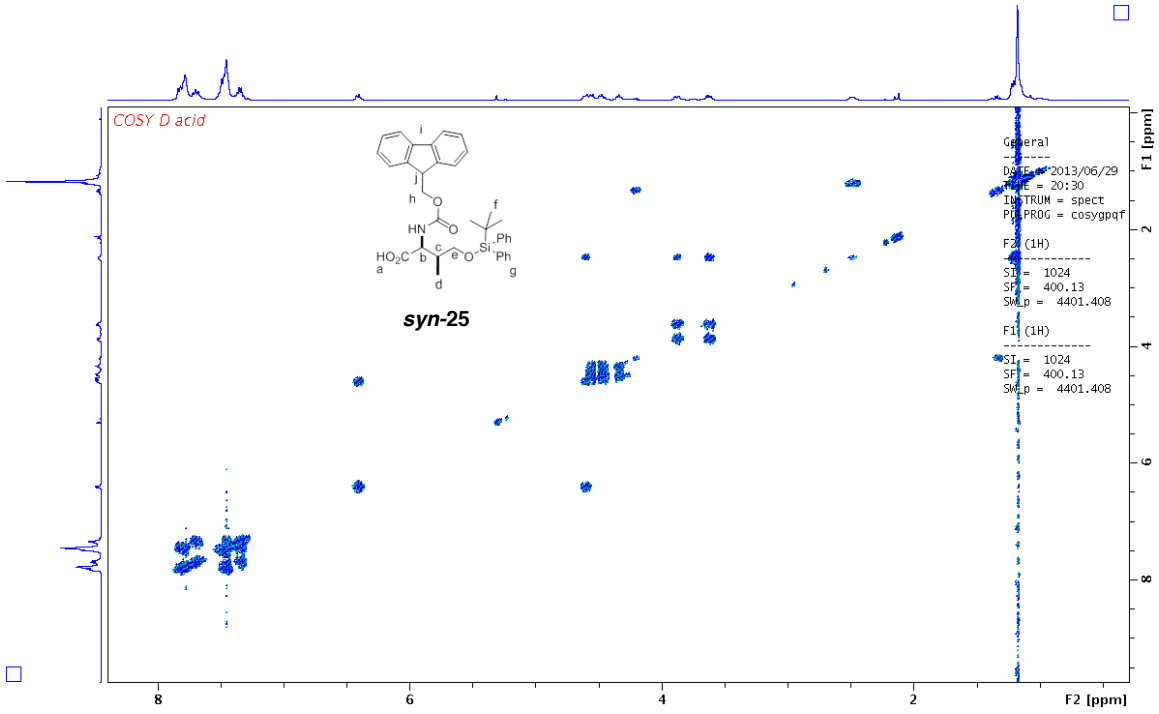
(2*S*,3*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((*tert*-butyldiphenyl-silyl)oxy)-3-methylbutanoic acid (*syn*-25);

Purification by flash chromatography afforded *syn*-**25** as a white foamy solid (0.42 g, 49 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.60 (8H, m), 7.55 – 7.29 (10H, m), 6.41 (1H, d, *J* = 8.4 Hz), 4.61 – 4.51 (7H, m), 4.34 (1H, t, *J* = 6.9 Hz), 3.88 (1H, d, *J* = 8.5 Hz), 3.62 (1H, dd, *J* = 10.7, 5.1 Hz), 2.49 (1H, m), 1.25 – 1.09 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.9, 143.9, 141.3, 135.7, 132.6, 130.0, 127.9, 127.7, 127.1, 125.3, 120.0, 67.4, 66.1, 58.1, 47.1, 36.4, 26.9, 19.2, 14.7. IR (CH_2Cl_2) n (cm^{-1}) 3399, 3067, 2928, 1717, 1508, 1450, 1427, 1219, 1111, 1034. HRMS (ESI): Exact mass calcd for $C_{36}H_{39}NaNO_5Si$ *ie* $[M+Na]^+$ 616.2495. Found 616.2552.

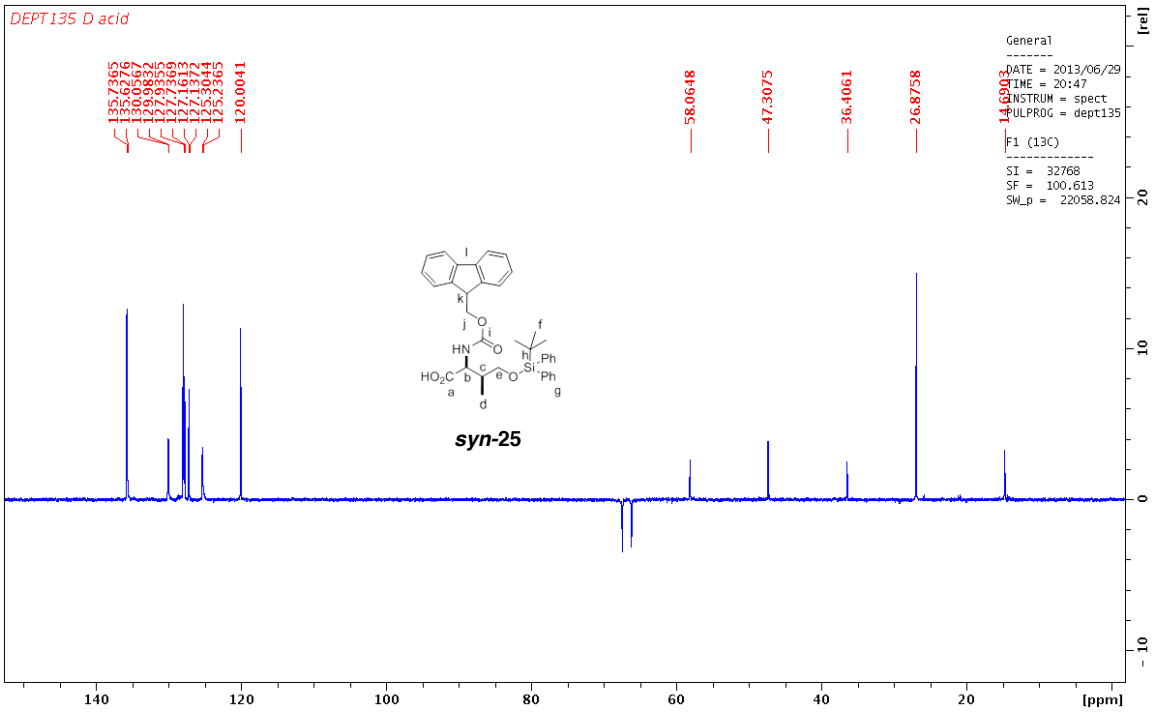


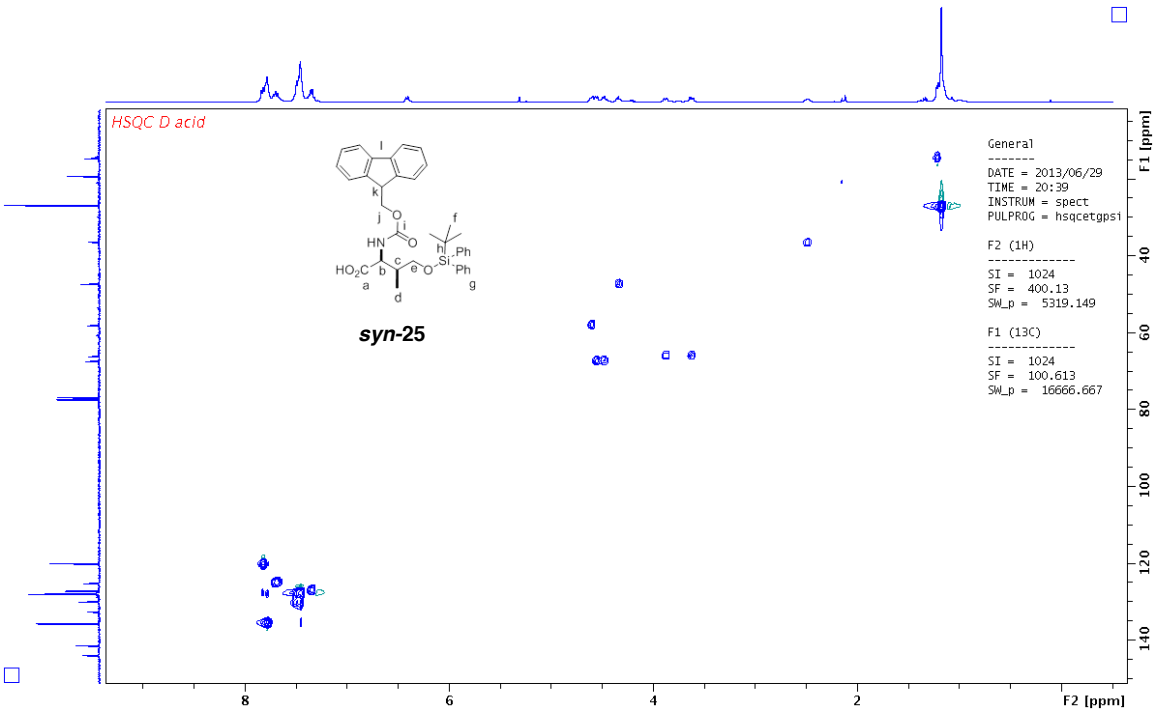


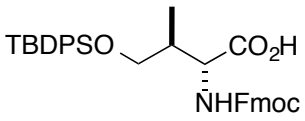
***syn*-25**



***syn*-25**


DEPT135 D acid
135.7365
135.6776
130.0567
129.9832
127.9355
127.7369
127.1913
127.1172
125.3044
125.2365
120.0041
58.0648
47.3075
36.4061
26.8758
14.6903
General
DATE = 2013/06/29
TIME = 20:47
INSTRUM = spect
PULPROG = dept135
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
[rel]
syn-25
[ppm]

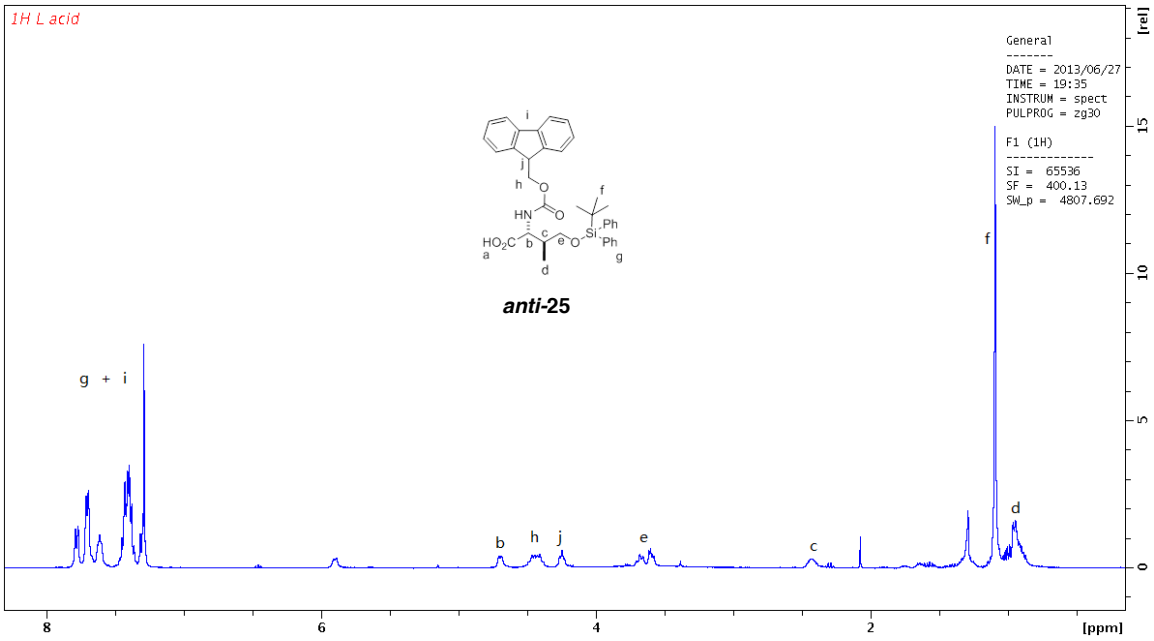

HSQC D acid
General
DATE = 2013/06/29
TIME = 20:39
INSTRUM = spect
PULPROG = hsqcetgpsi
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 5319.149
F1 (13C)
SI = 1024
SF = 100.613
SW_p = 16666.667
syn-25
F1 [ppm]
F2 [ppm]

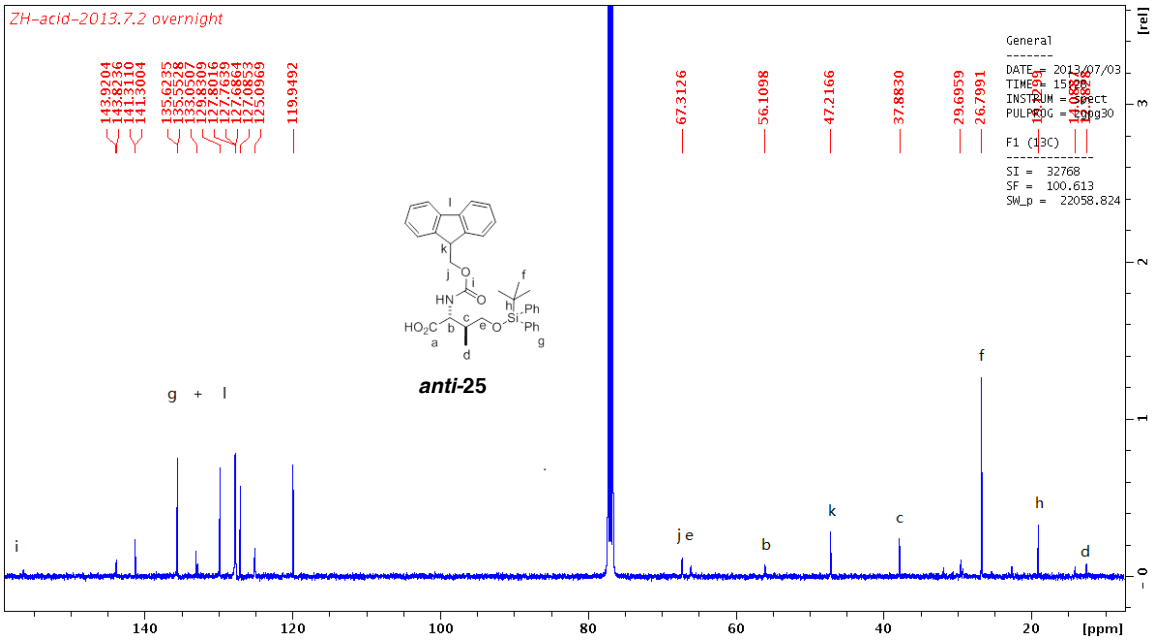


anti-**25**

(2*R*,3*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((*tert*-butyldiphenyl-silyl)oxy)-3-methylbutanoic acid (*anti*-25);

Purification by flash chromatography afforded *anti*-**25** as a white foamy solid (0.34 g, 40 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.56 (8H, m), 7.49 – 7.27 (10H, m), 5.90 (1H, d, J = 8.2 Hz), 4.69 (2H, d, J = 6.2 Hz), 4.51 – 4.34 (2H, m), 4.24 (1H, t, J = 6.5 Hz), 3.70 – 3.57 (2H, m), 2.43 (1H, br), 1.09 (9H, s), 0.95 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 143.8, 141.3, 135.6, 133.0, 129.8, 127.8, 127.7, 127.1, 125.1, 119.9, 67.3, 66.1, 56.1, 47.2, 37.9, 29.7, 26.8, 19.1. HRMS (ESI): Exact mass calcd for $C_{36}H_{40}NO_5Si$ *ie* $[M+H]^+$ 594.2676. Found 594.2752.



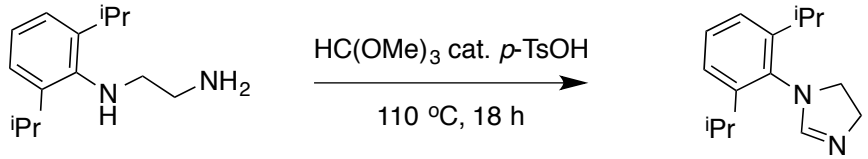

ZH-acid-2013.7.2 overnight
143.9204
143.8236
141.3110
141.3004
135.6235
135.5528
133.0507
129.8309
127.8016
127.7234
127.6854
127.0853
125.0969
119.9492
67.3126
56.1098
47.2166
37.8830
29.6959
26.7991
19.2691
14.0824
14.0688
General
DATE_ = 2013/07/03
TIME_ = 15:57
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 22058.824
anti-25
g + l
i
j e
b
k
c
f
h
d
[ppm]
[rel]

APPENDIX D
EXPERIMENTAL FOR CHAPTER IV

A. Preparation of compounds R – S, 26a and c and 1a and c.

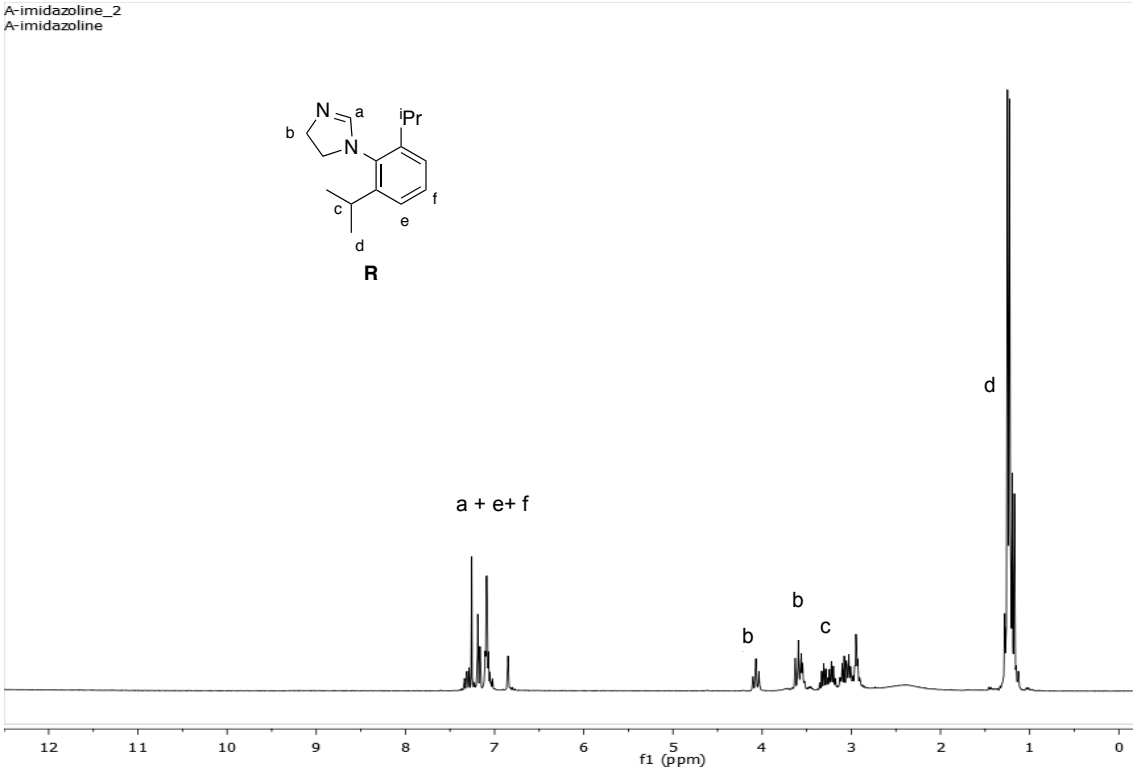
Calculations were performed as previously described.[32,35]

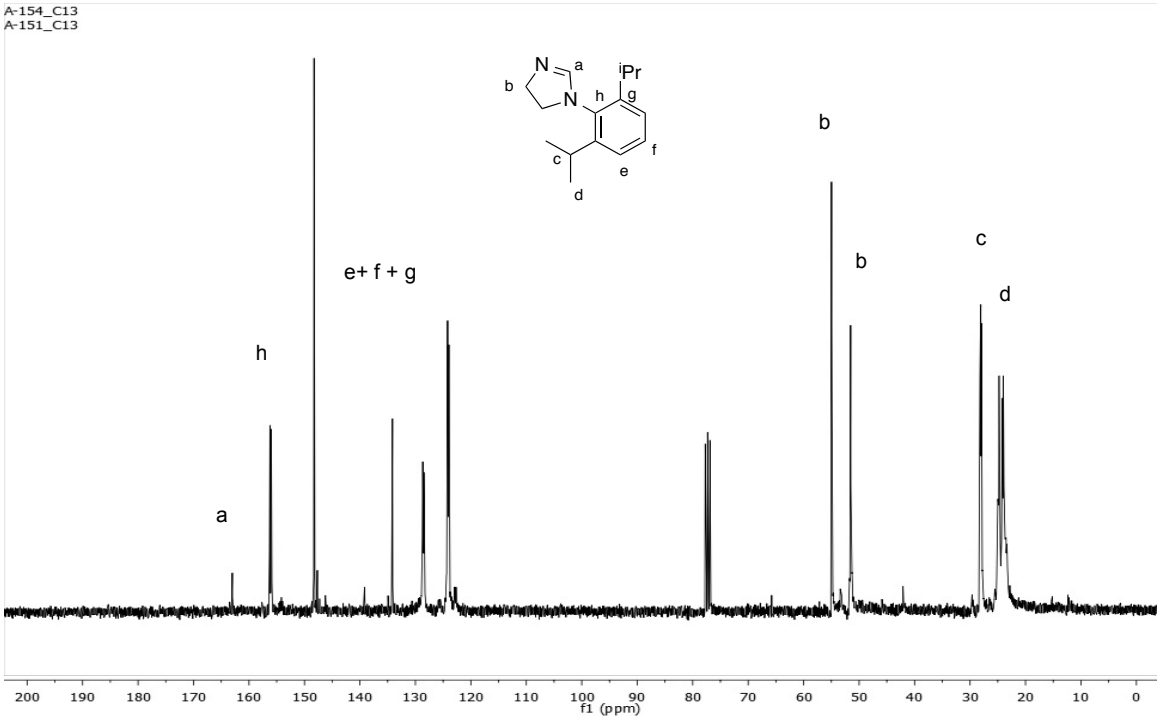
Preparation of 1-(2,6-Diisopropylphenyl)-4,5-dihydro-imidazole R.



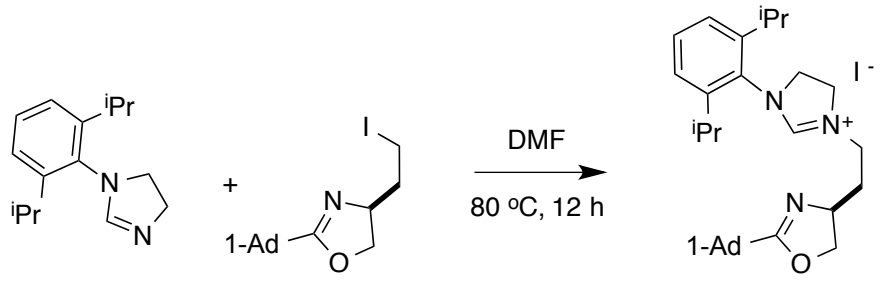
R
45 %

N-(2,6-Diisopropylphenyl)ethane-1,2-diamine (2.20 g, 10 mmol) was dissolved in 10 mL of trimethyl orthoformate. Catalytic amount of *p*-toluenesulfonic acid (0.10 g, 0.5 mmol) was added to solution then the mixture was refluxed using an air condenser to allowed methanol to escape until completion (18 h). Solvent was removed under reduce pressure and the residue was purified by recrystallization (CH_2Cl_2/hexane) to obtained **R** (1.04 g, 4.5 mmol, 45%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.16 (3H, m) 6.82 (1H, s), 4.06 (2H, t, J = 8.7 Hz), 3.58 (2H, t, J = 10.2 Hz), 3.11-3.04 (2H, m), 1.23 (6H, d, J = 6.9 Hz), 1.18 (6H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 156.2, 155.9, 148.2, 134.1, 128.6, 124.1, 55.0, 51.6, 28.3, 28.0, 25.3, 24.5, 23.9, 23.5. IR (Thin film, cm^{-1}) 3364, 3206, 3063, 3024, 2963, 2928, 2866, 1678, 1605, 1585, 1458, 1381, 1366, 1327, 1265, 1204, 1180, 1107, 1053, 961, 933, 887. HRMS (ESI, TOF): Exact mass calcd for $C_{15}H_{22}N_2$ *ie* $[M+H]^+$ 231.1861. Found. 231.1835.


A-imidazoline_2
A-imidazoline
N
a
b
N
iPr
c
d
e
f
R
a + e+ f
b
b
c
d
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

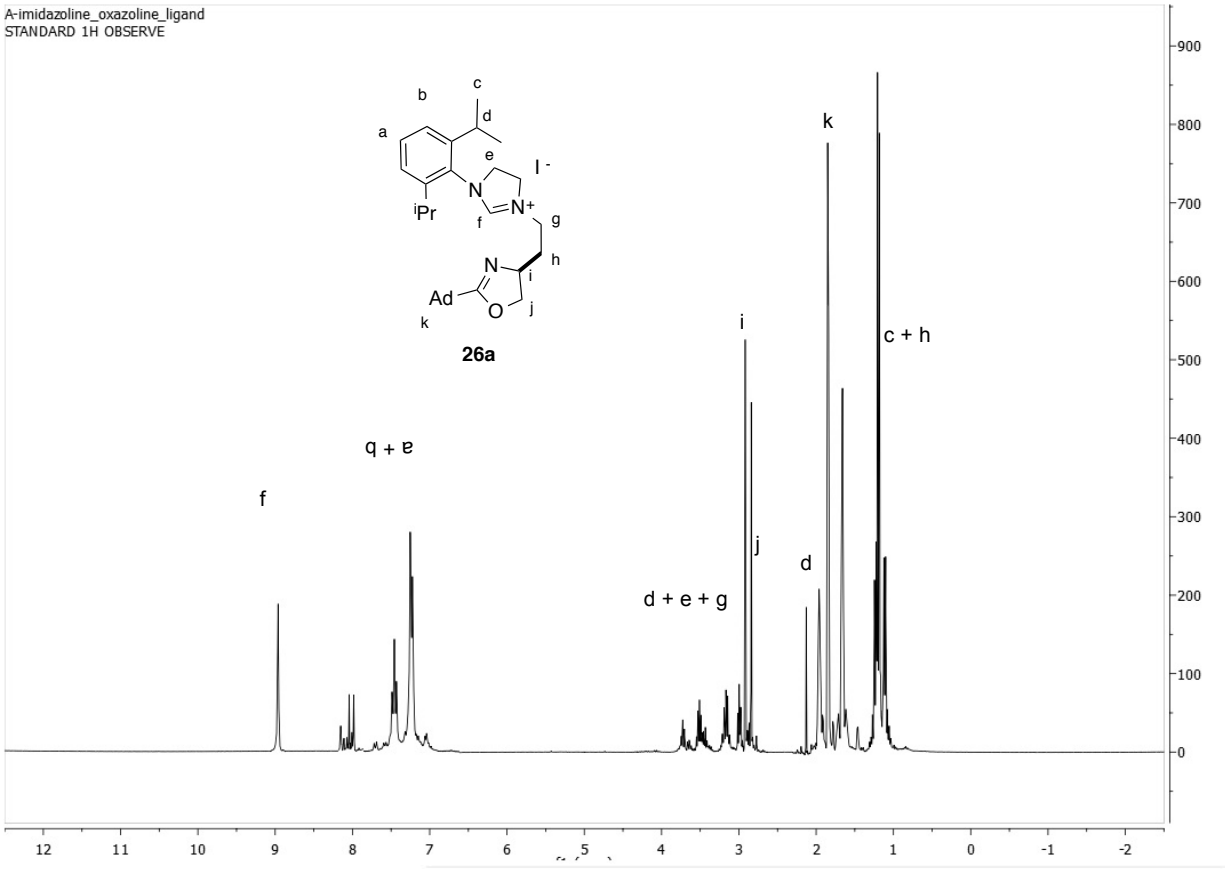

A-154_C13
A-151_C13
N
a
b
N
h
iPr
g
c
d
e
f
a
h
e+ f + g
b
b
c
d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

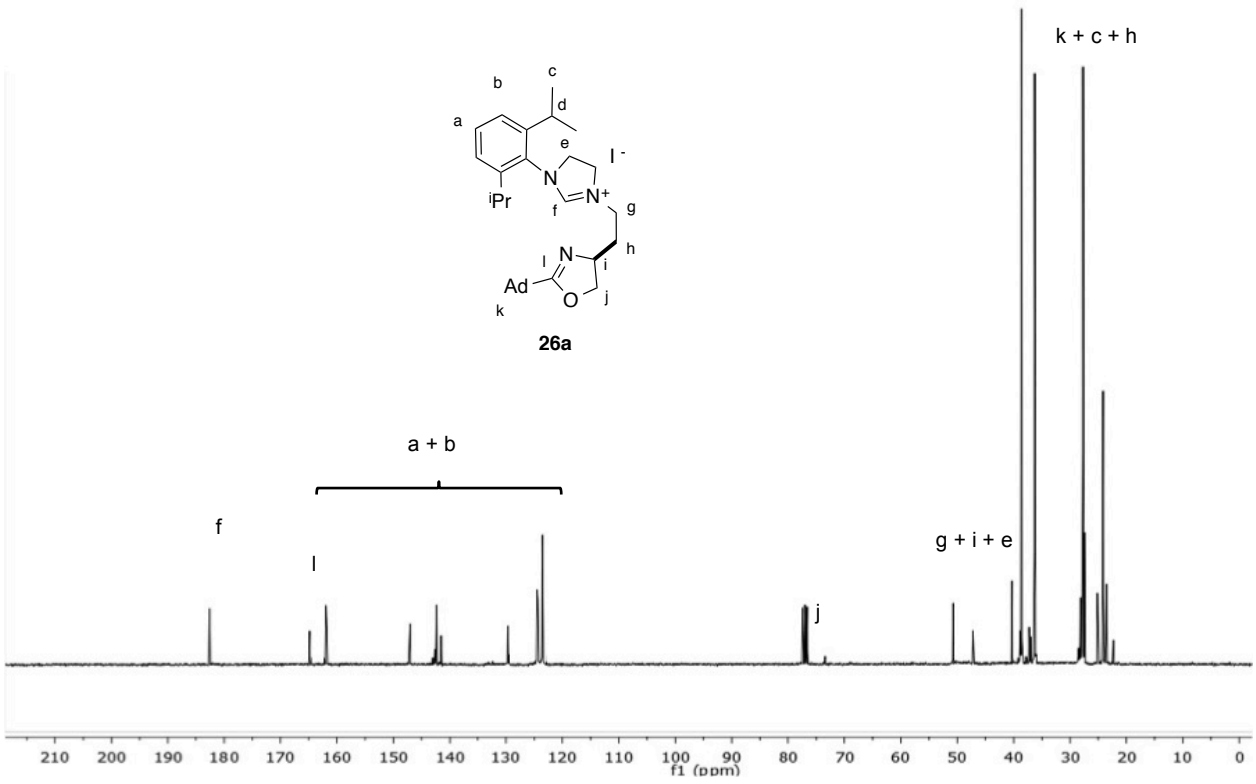
Preparation of (*S*)-3-(2-(2-(Adamantan-1-yl)-4,5-dihydrooxazol-4-yl)ethyl)-1-(2,6-diisopropylphenyl)-4,5-dihydro-imidazolium Iodide 26a.



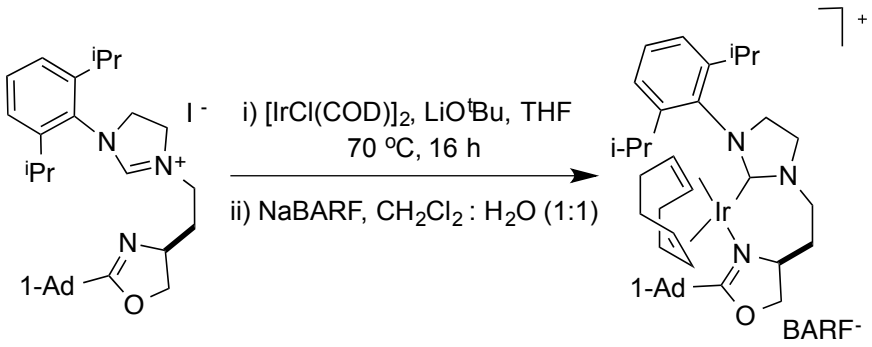
R **26a** 98 %

(*S*)-2-(Adamantan-1-yl)-4-(2-iodoethyl)-4,5-dihydrooxazole (1.80 g, 5 mmol) and 1-(2,6-diisopropylphenyl)-4,5-dihydro-imidazole **R** (1.15 g, 5 mmol) was dissolved in 10 mL of DMF under Ar atmosphere. The mixture was heated to 80 ^{o}C for 12 h. The solvent was removed under reduced pressure and the residue was washed with Et_2O (5 × 5 mL) to yield compound **26a** (2.89 g, 4.9 mmol, 98%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.0 (1H, s), 8.05-8.01 (1H, m), 7.49-7.40 (2H, m), 7.31-7.20 (1H, m), 3.79 (2H, m), 3.57-3.46 (3H, m), 3.45-3.23 (1H, m), 2.92-2.70 (3H, m), 2.37 (1H, s), 1.91-1.54 (15H, m), 1.27-1.00 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ. 183.6, 166.1, 162.8, 161.9, 147.0, 144.5, 143.9, 142.7, 142.3, 129.6, 124.4, 123.4, 122.5, 73.4, 50.7, 47.2, 20.3, 38.9, 38.6, 37.3, 36.4, 28.2, 28.0, 27.4, 25.1, 24.1, 23.5, 22.3. IR (Thin film, cm^{-1}) 3066, 2978, 2922, 2844, 1610, 1602, 1458, 1352, 1268, 1161, 1131, 998, 931. HRMS (ESI, TOF): Exact mass calcd for $C_{30}H_{44}N_3O^+$ *ie* $[M]^+$ 462.3479. Found 462.3487.


A-imidazoline_oxazoline_ligand
STANDARD 1H OBSERVE
26a
f
q + e
d + e + g
j
d
i
k
c + h


26a
k + c + h
a + b
f
l
j
g + i + e

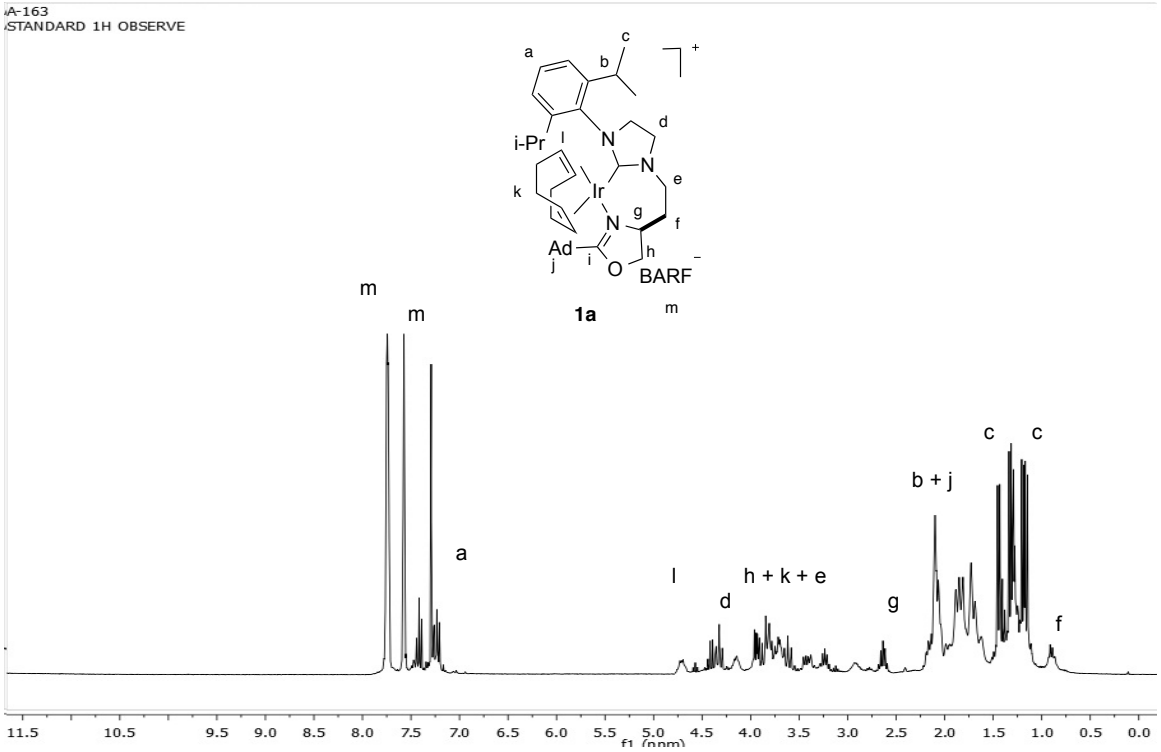
Synthesis of (η^4-1,5-Cyclooctadiene)(1-[(4*S*)-(2-(1-adamantyl) -4-5-dihydrooxazolyl)-ethyl]-3-(2,6-diisopropylphenyl)-4,5-dihydro-imidazolin-2-ylidene)iridium(I) Tetrakis(3,5- bis(trifluoromethyl)phenyl)borate 1a.

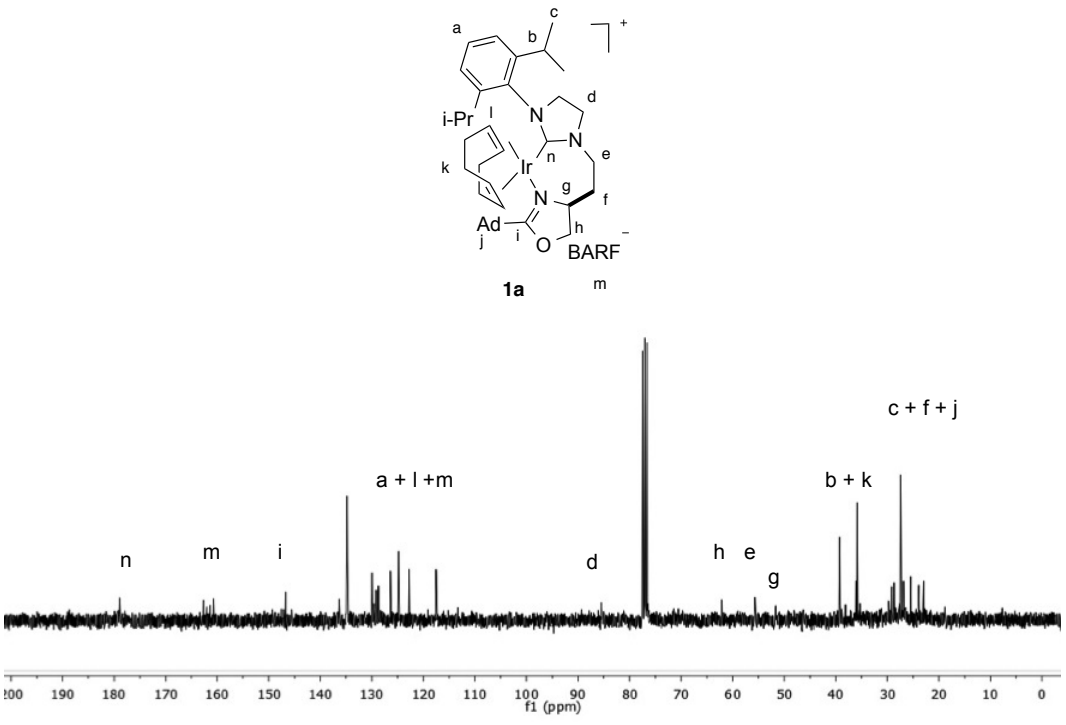


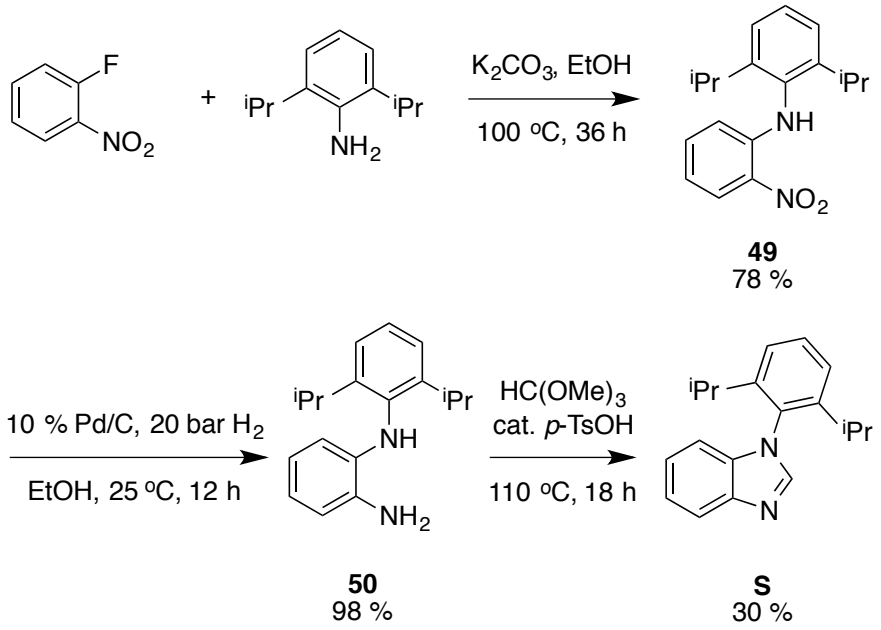
26a **1a** 55 %

(*S*)-3-(2-(2-(Adamantan-1-yl)-4,5-dihydrooxazol-4-yl)ethyl)-1-(2,6-diisopropyl-phenyl)-4,5-dihydro-imidazolium iodide **26a** (1 mmol) was added to a round bottom flask along with 1.5 equivalents lithium *tert*-butoxide and 0.5 equivalents of $[Ir(COD)Cl]_2$ under Ar. THF was syringed in to make the solution 0.03 M in imidazolinium salt. The mixture was heated to 70 ^oC in an oil bath and stirred for 16 h. After cooling to room temperature, the volatiles were removed under reduced pressure and 1.5 equivalents of NaBARF in 5 mL CH_2Cl_2 was added. Water (5 mL) was added and the mixture was stirred vigorously for 15 min. The organic layer was removed and the aqueous layer was washed with an additional 5 mL CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4) and the volatiles were removed in *vacuo*. The residue was chromatographed using a short silica column and 10 % hexane/CH_2Cl_2 as the eluent to obtain compound **1a** (55 %). mp. 79.8-80.4 (decompose). ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (8H, s), 7.57 (4H, s), 7.41-7.39 (1H, m), 7.28-7.20 (2H, m), 4.73-4.68 (1H, m), 4.41-4.29 (2H, m), 4.16-4.12 (1H, m), 3.97-3.58 (6H, m), 3.46-3.38 (1H, m), 3.25-3.21 (1H, m), 2.95-2.89 (1H, m), 2.68-2.59 (1H, m), 2.17-1.59 (20H, m), 1.45-1.15 (16H, m), 0.95-0.84 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ. 178.4, 177.5, 174.5, 163.6, 162.7, 162.0, 161.3, 160.7, 146.7, 136.3, 134,9, 134.8, 130.0, 129.2, 129.1, 128.7 (2 peaks), 128.6, 126.4, 124.8, 122.7, 117.5, 85.5, 62.1, 55.7, 39.3, 36.1, 29.1, 28.7, 27.4, 26.9,

25.4, 23.9, 22.9. IR (Thin film, cm^{-1}) 3067, 2967, 2916, 2851, 1609, 1606, 1458, 1354, 1277, 1161, 1126, 999, 929, 887. HRMS (ESI, TOF): Exact mass calcd for $C_{38}H_{55}IrN_3O^+$ *ie* $[M]^+$ 762.3969. Found 762.3954 and $C_{32}H_{12}BF_{24}^-$ *ie* $[M]^-$ 863.0654. Found 863.0632.



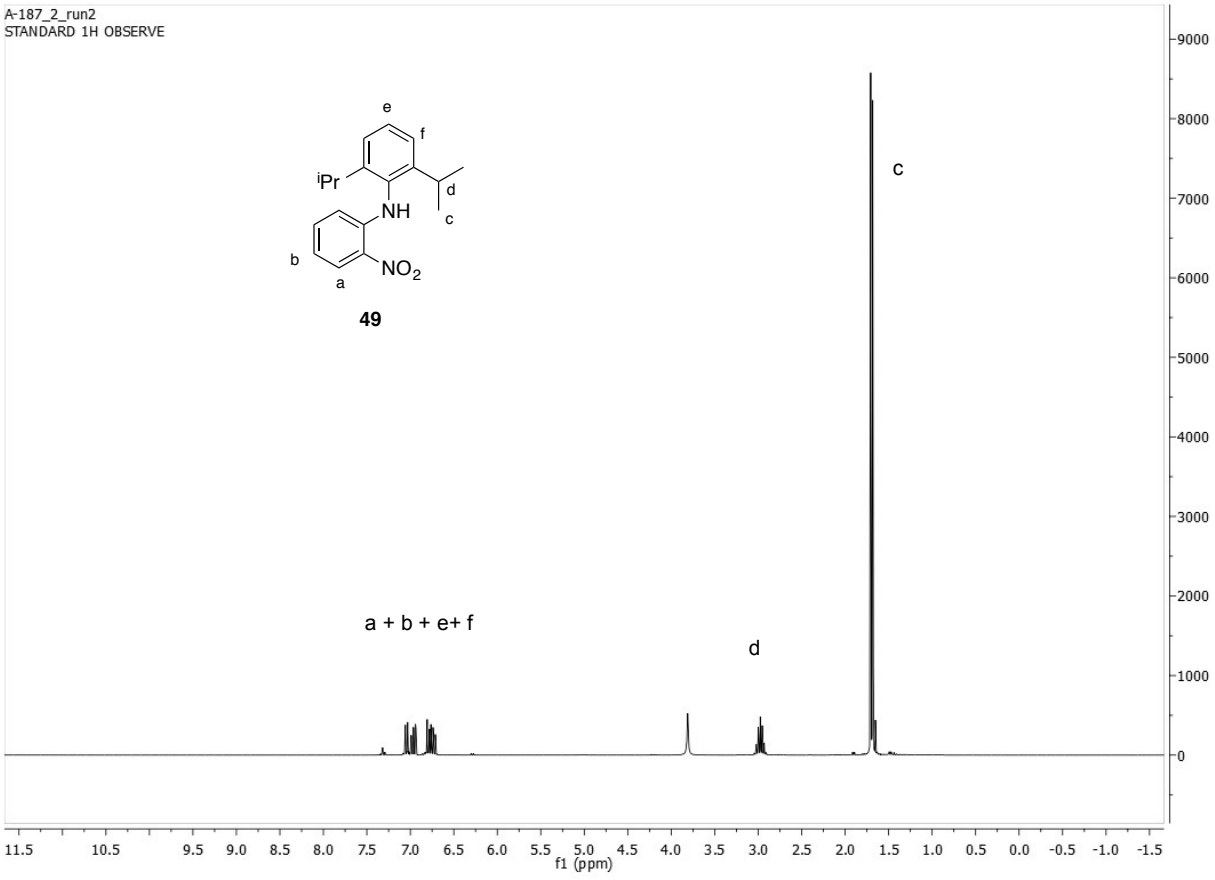


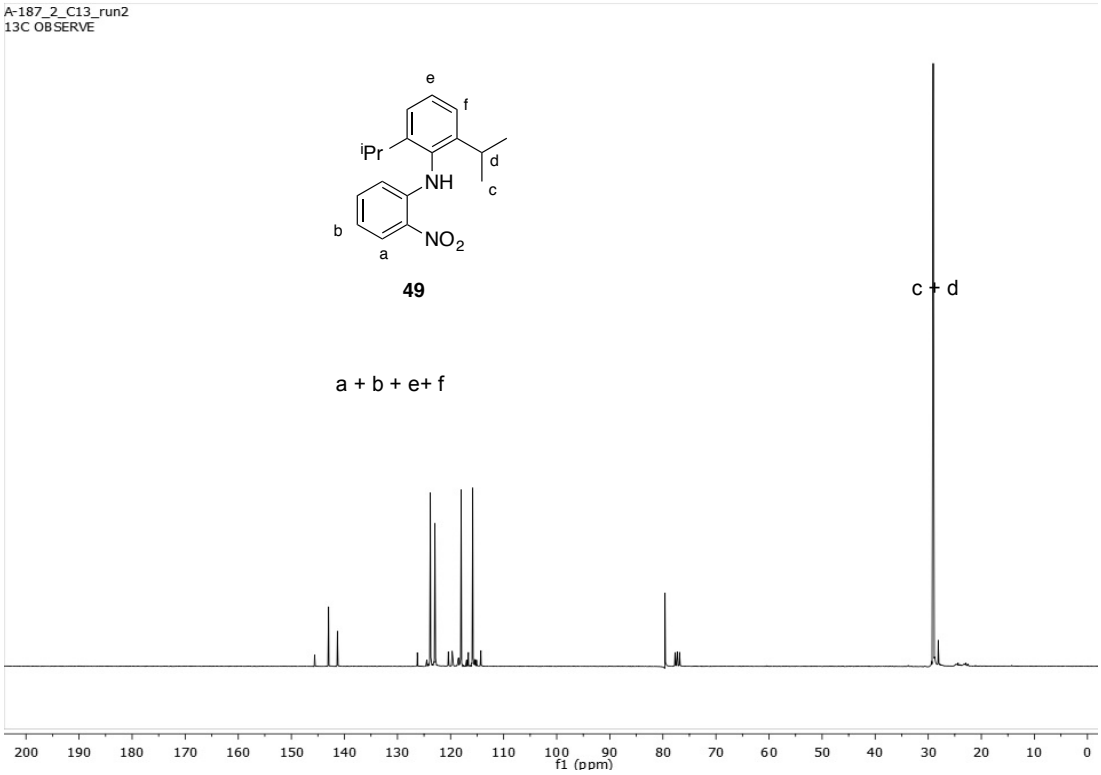


Preparation of 2,6-Diisopropyl-*N*-(2-nitrophenyl)aniline 49.

2-Fluoronitrobenzene (1.41 g, 10 mmol) was added into solution of K_2CO_3 (2.76 g, 20 mmol) and 2,6-diisopropylaniline (4.43 g, 20 mmol) in 30 mL of ethanol. The

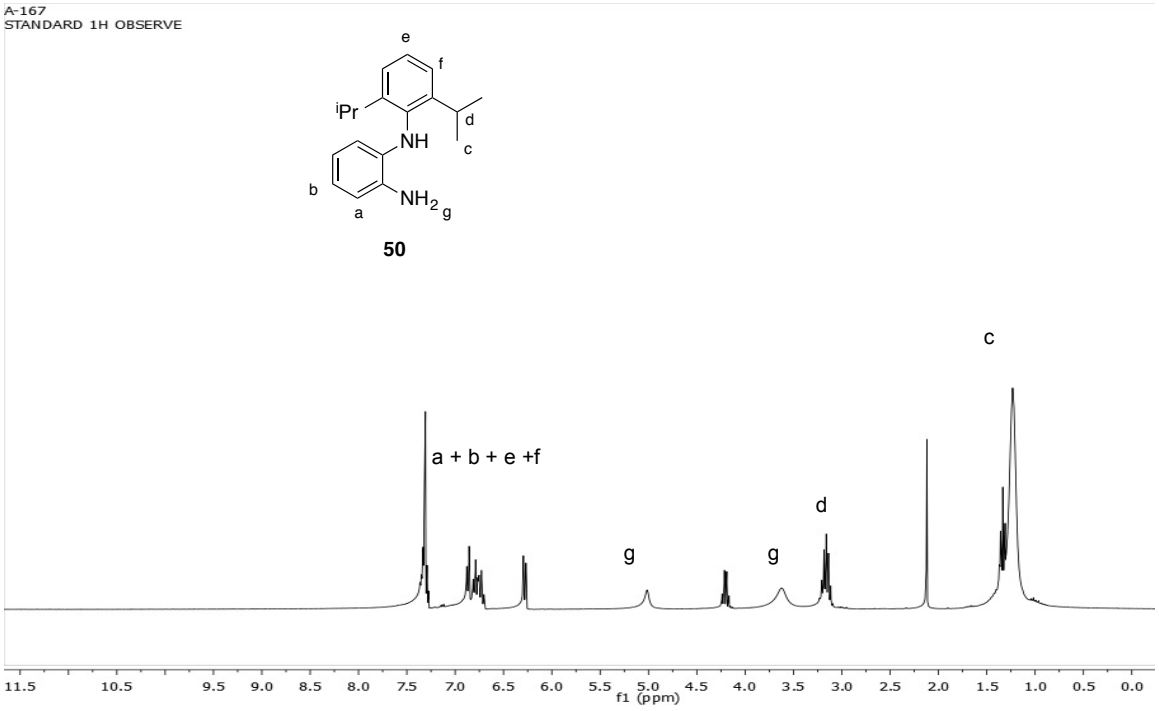
mixture was refluxed until completion (36 h). The mixture was allowed to cool to ambient temperature then filtered through celite. Solvent was removed under reduced pressure, and the crude products were chromatographed using 5% CH_2Cl_2/hexane to yield **49** (2.27 g, 7.6 mmol, 76%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (2H, d, J = 7.8 Hz), 6.98 (1H, t, J = 7.5 Hz), 6.70-6.45 (4H, m), 3.65 (1H, br), 3.05-2.96 (2H, m), 1.34 (12H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ. 145.6, 143.0, 141.3, 126.3, 124.5, 123.8, 120.4, 118.6, 118.0, 116.6, 115.8, 114.3, 79.6, 29.1. HRMS (ESI, TOF): Exact mass calcd for $C_{18}H_{22}N_2O_2$ *ie* $[M+H]^+$ 299.1760. Found 299.1733.

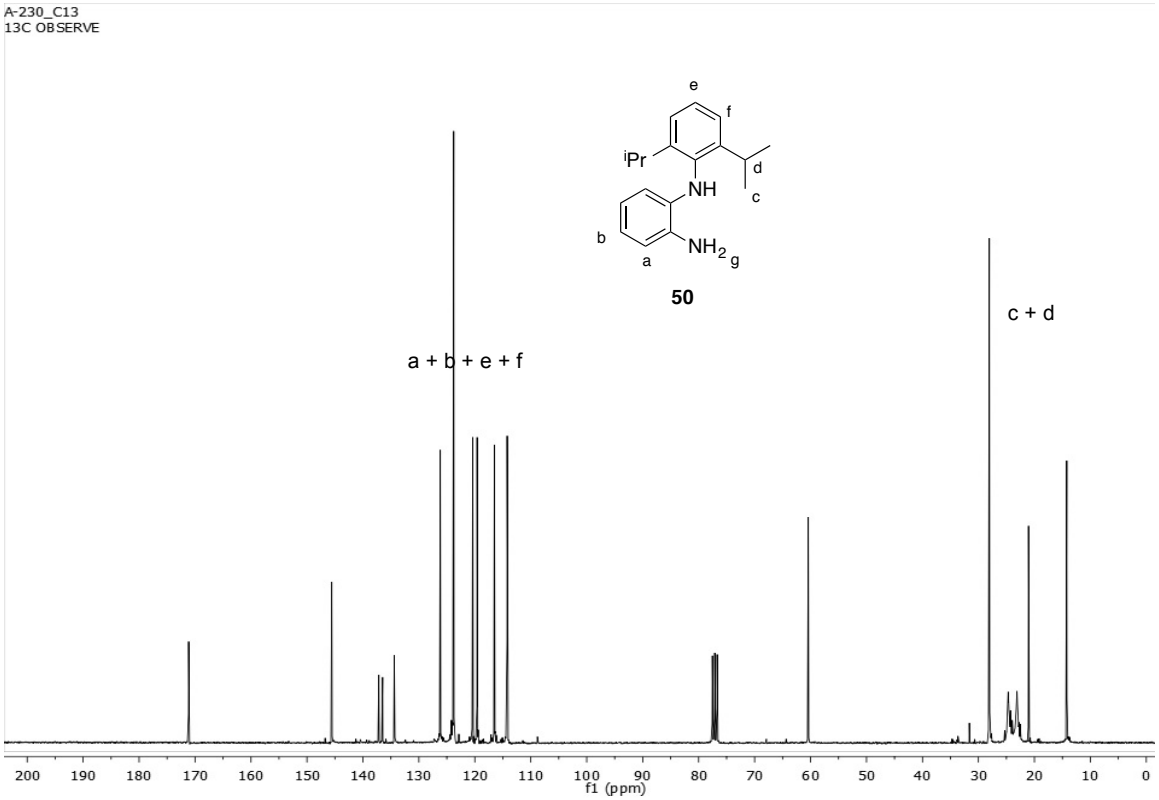




Preparation of *N*-(2,6-Diisopropylphenyl)benzene-1,2-diamine 50.

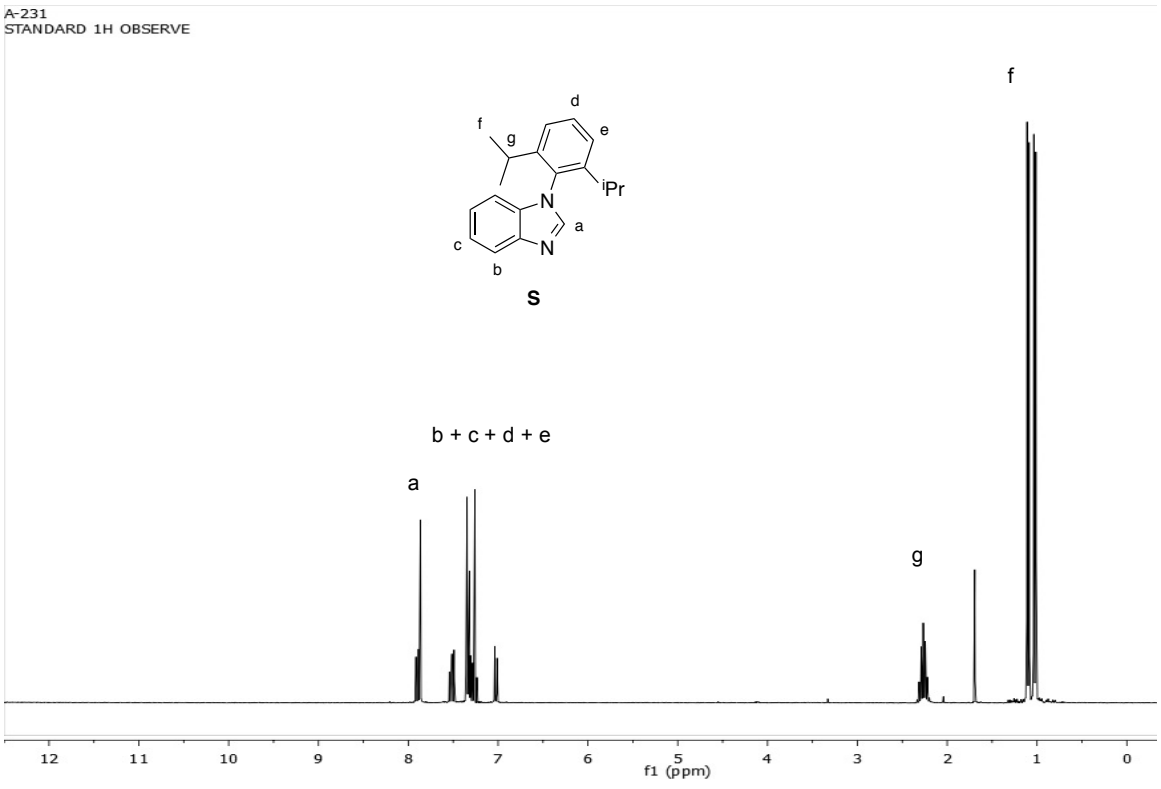
10 % Pd/C (0.02 g, 0.02 mmol) was added to solution of 2,6-diisopropyl-*N*-(2-nitrophenyl)aniline **49** (0.65 g, 2 mmol) in 15 mL of EtOH. The mixture was then placed into steel pressure bomb and then flushed with H_2. The reaction was stirred under 20 bar of H_2 for 12 h. The mixture was passed through celite and the solvent was removed under reduced pressure to yield compound **50** (0.52 g, 1.96 mmol, 98%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.29 (3H, m), 6.88-6.76 (3H, m), 6.29-6.26 (1H, m), 5.01 (1H, br), 3.60 (2H, br), 3.21-3.12 (2H, m), 1.37-1.23 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 137.2, 136.5, 134.4, 126.2, 123.8, 120.4,119.6, 116.5, 114.2, 28.0, 14.2. HRMS (ESI, TOF): Exact mass calcd for $C_{18}H_{24}N_2$ *ie* $[M+2H]^{2+}$ 135.1043. Found 135.1054.

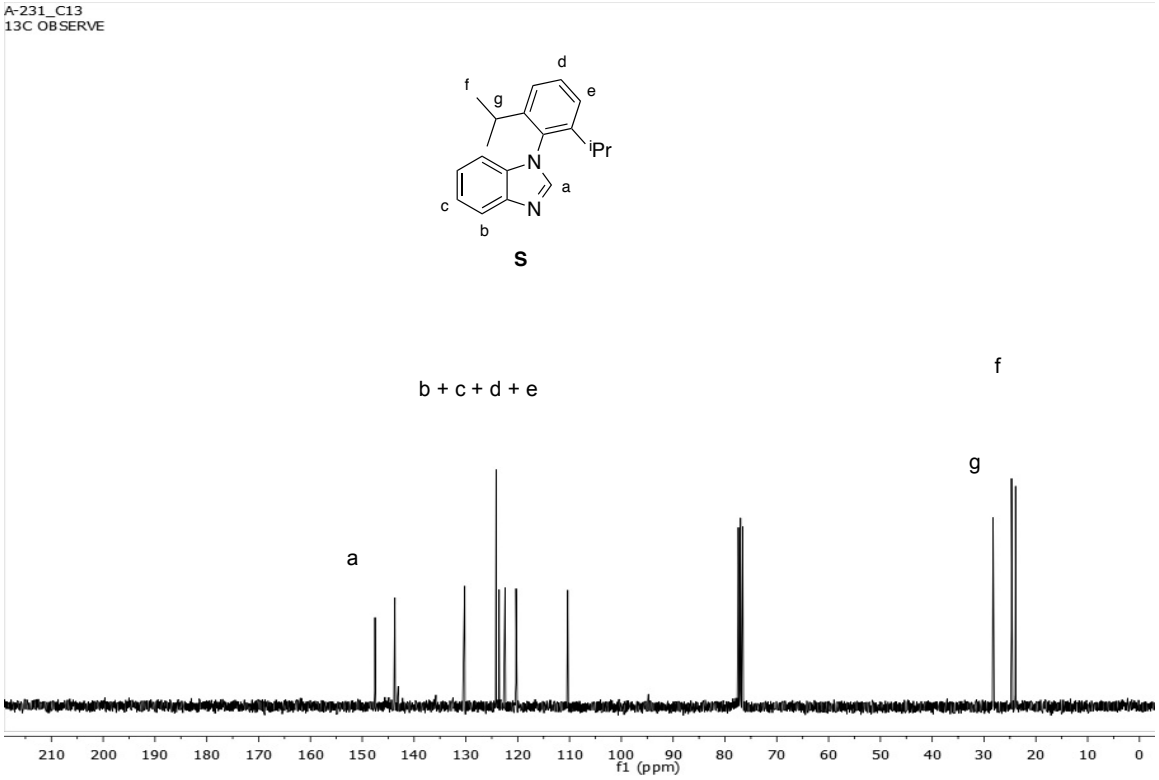

A-167
STANDARD 1H OBSERVE
e
f
iPr
d
c
NH
b
a
NH2
g
50
c
a + b + e +f
g
g
d
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


A-230_C13
13C OBSERVE
e
f
iPr
d
c
NH
b
a
NH2
g
50
c + d
a + b + e + f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

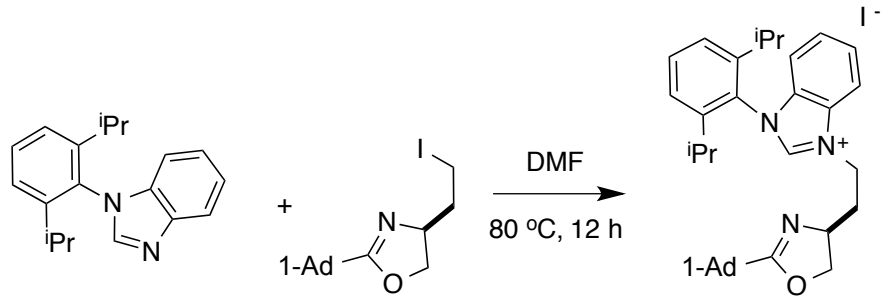
Preparation of 1-(2,6-Diisopropylphenyl)-benzo[*d*]-imidazole S.

N-(2,6-Diisopropylphenyl)benzene-1,2-diamine **50** (0.60 g, 2.3 mmol) was dissolved in 5 mL of trimethyl orthoformate. Catalytic amount of *p*-toluenesulfonic acid (0.002 g, 0.01 mmol) was added to solution then the mixture was refluxed using air condenser to allow methanol to escape until completion (18 h). Solvent was removed under reduce pressure and the residue was purified by recrystallization (CH_2Cl_2/hexane) to obtained **S** (0.19 g, 0.69 mmol, 30%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.55-7.53 (1H, m), 7.38-7.24 (5H, m), 7.08-7.05 (1H, m), 2.34-2.25 (2H, m), 1.13 (6H, d, J = 6.9 Hz), 1.06 (6H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 143.7, 143.1, 130.6, 130.2, 124.2, 123.6, 122.4, 120.3, 110.3, 28.3, 24.7, 23.9. IR (Thin film, cm^{-1}) 3429, 3075, 2963, 2928, 2870, 1643, 1612, 1593, 1485, 1462, 1385, 1366, 1308, 1281, 1223, 1142, 1057, 1007, 976, 934, 887. HRMS (ESI, TOF): Exact mass calcd for $C_{19}H_{22}N_2$ *ie* $[M+H]^+$ 279.1861. Found 279.1863.





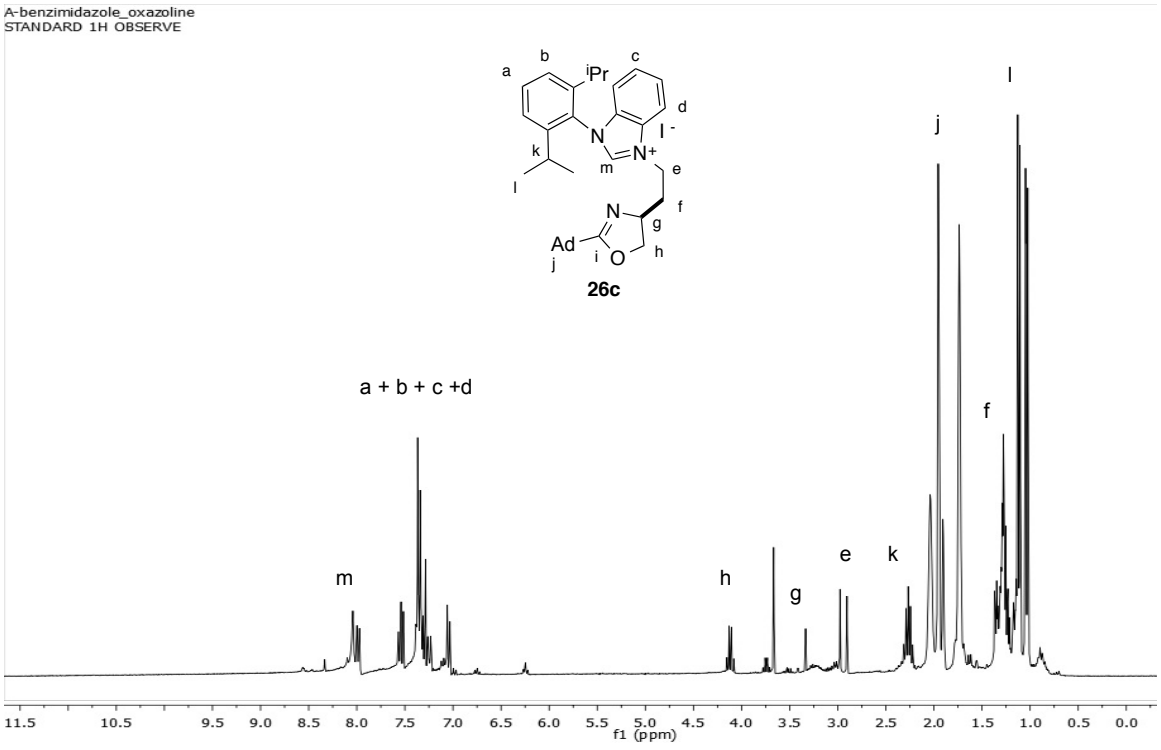
Preparation of (*S*)-3-(2-(2-(Adamantan-1-yl)-4,5-dihydrooxazol-4-yl)ethyl)-1-(2,6-diisopropylphenyl)benzo[*d*]imidazolium Iodide 26c.

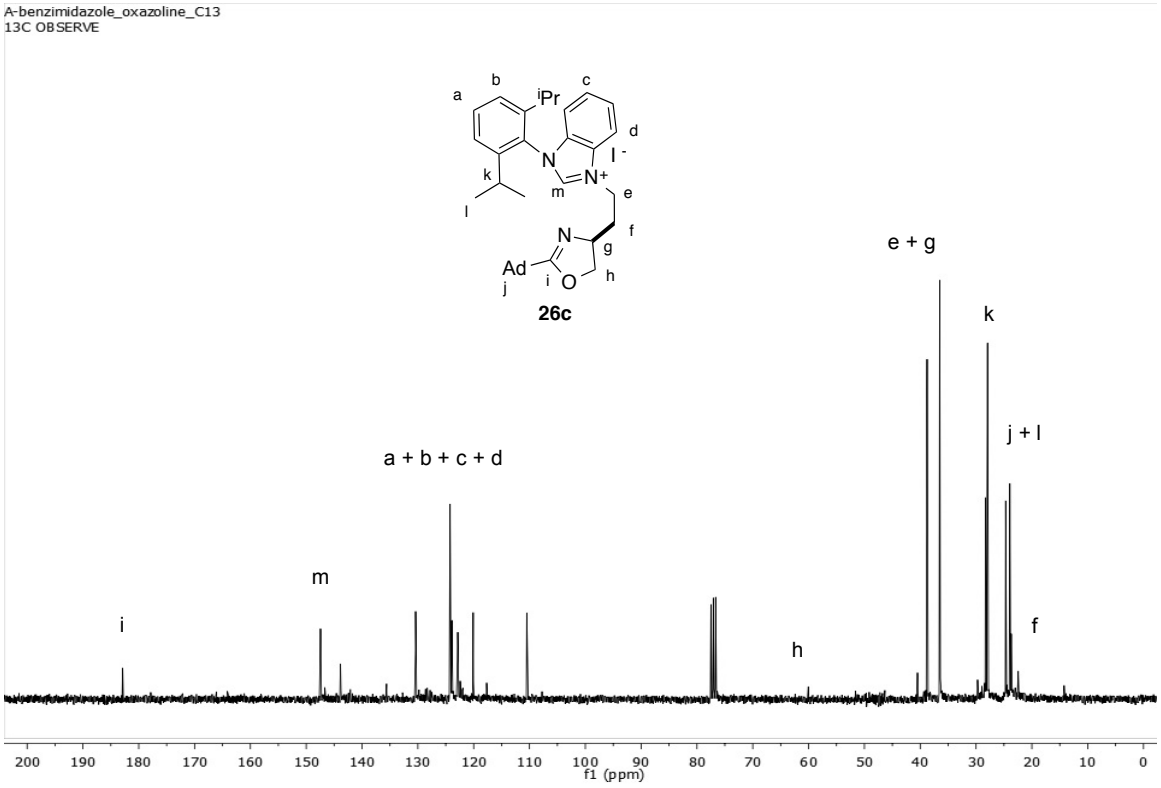


S **26c**
75 %

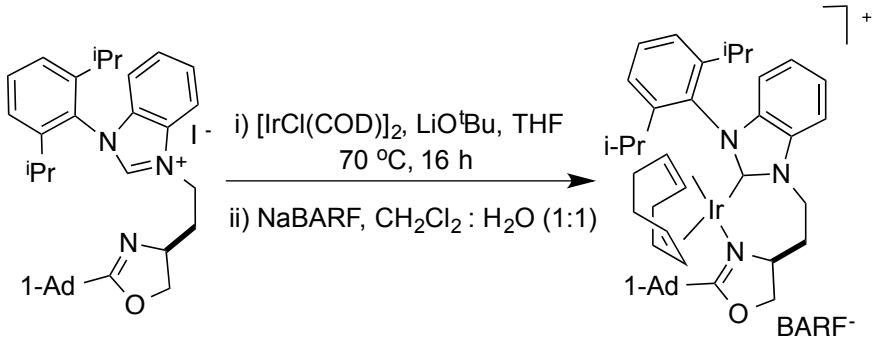
(*S*)-2-(Adamantan-1-yl)-4-(2-iodoethyl)-4,5-dihydrooxazole (1.80 g, 5 mmol) and 1-(2,6-diisopropylphenyl)-benzo[*d*]imidazole **S** (1.39 g, 5 mmol) was dissolved in 10 mL of DMF under Ar atmosphere. The mixture was heated to 80 °C for 12 h. The solvent was removed under reduced pressure and the residue was washed with Et_2O (5 ×

5 mL) to yield compound **26c** (2.39 g, 3.8 mmol, 75%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, s), 8.06-7.99 (1H, m) 7.57-7.22 (5H, m), 7.06-7.03 (1H, m), 4.15-4.08 (1H, m), 2.97-2.90 (2H, m), 2.29-1.74 (14H, m), 1.37-1.21 (5H, m), 1.12 (6H, d, J = 6.9 Hz), 1.04 (6H, d, J = 6.9 Hz), 0.94-0.84 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 147.4, 146.7, 143.9, 135.6, 132.8, 130.4, 124.2, 123.9, 122.9, 120.1, 117.7, 110.5, 60.0, 51.8, 49.6, 49.1, 46.3, 40.5, 38.8, 36.5, 28.3, 27.9, 24.7, 23.9, 22.5, 22.4. IR (Thin film, cm^{-1}) 3065, 2977, 2915, 2853, 1615, 1605, 1454, 1352, 1267, 1161, 998, 934, 889. HRMS (ESI, TOF): Exact mass calcd for $C_{34}H_{44}N_3O^+$ *ie* $[M]^+$ 510.3479. Found 510.3499.



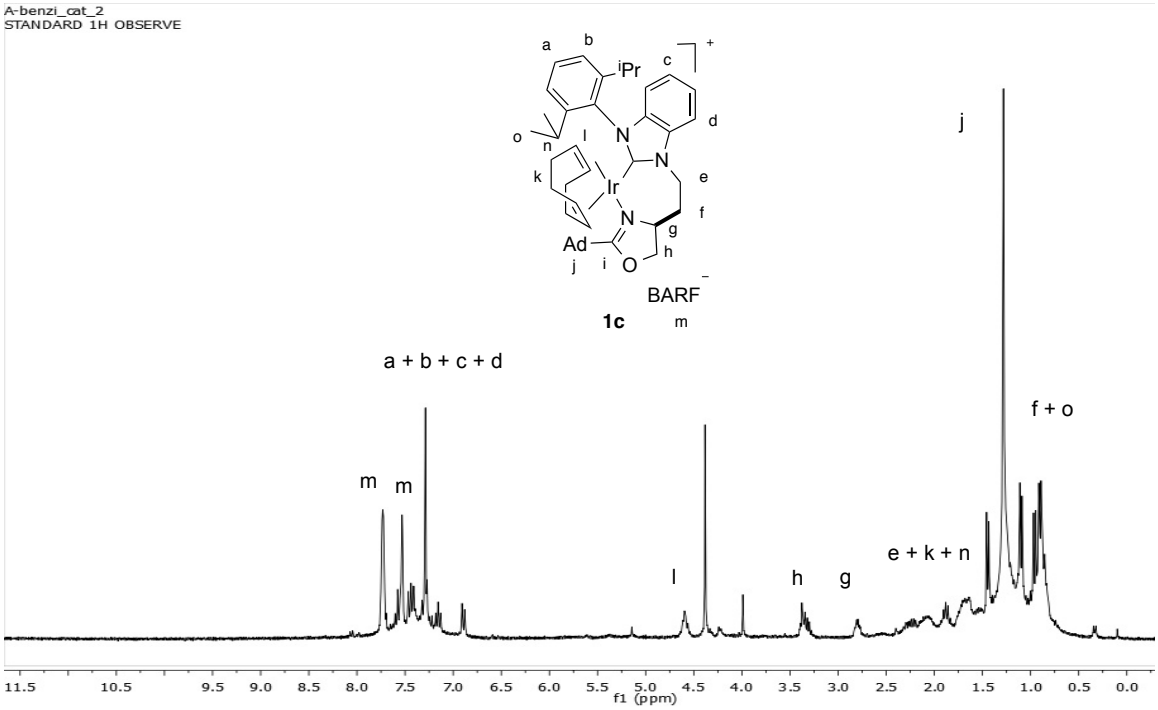


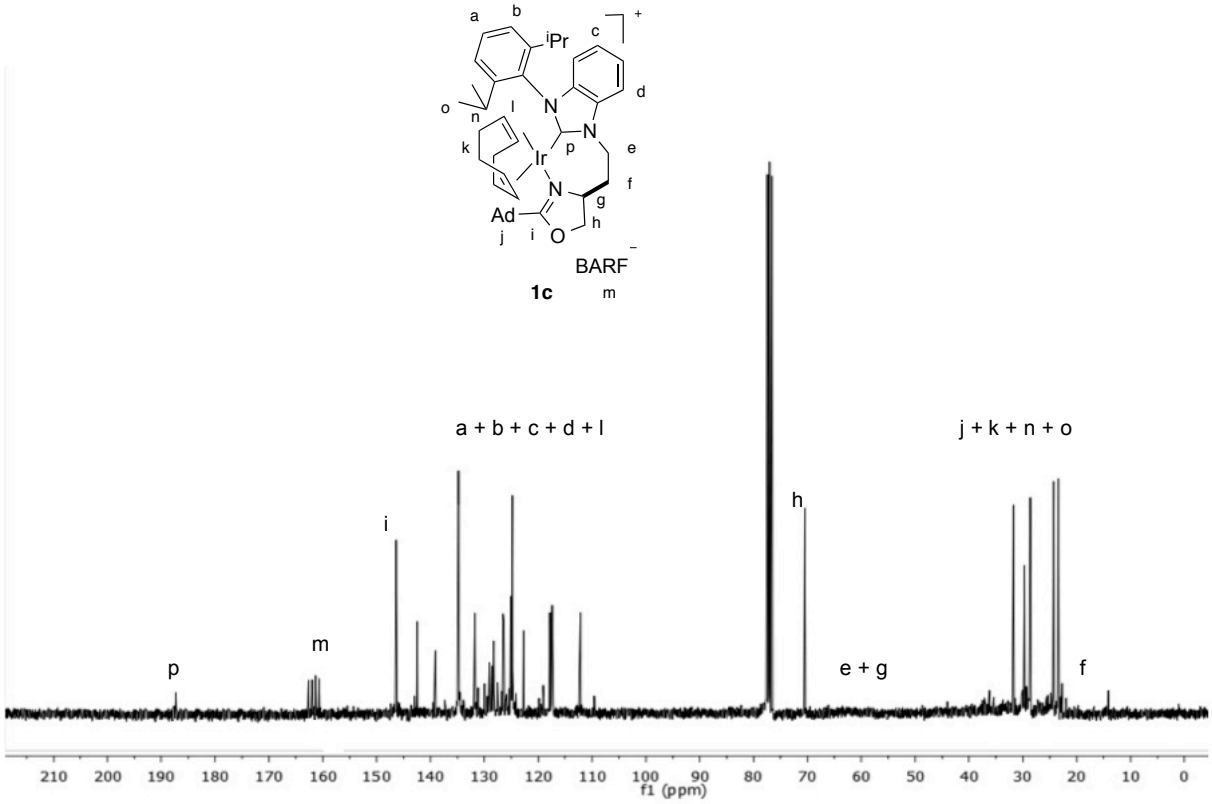
Synthesis of (η^4-1,5-Cyclooctadiene)(1-[(4*S*)-(2-(1-adamantyl)-4-5-dihydrooxazolyl)-ethyl]-3-(2,6-diisopropylphenyl)benzo[*d*]imidazol-2-ylidene)-iridium(I) Tetrakis(3,5- bis(trifluoromethyl)phenyl)borate 1c.



3 **1c** 48 %

(*S*)-3-(2-(2-(Adamantan-1-yl)-4,5-dihydrooxazol-4-yl)ethyl)-1-(2,6-diisopropyl-phenyl)-benzo[*d*]imidazol-3-ium iodide **26c** (1 mmol) was added to a round bottom flask along with 1.5 equivalents lithium *tert*-butoxide and 0.5 equivalents of $[Ir(COD)Cl]_2$ under Ar. THF was syringed in to make the solution 0.03 M in imidazolinium salt. The mixture was heated to 70 ^oC in an oil bath and stirred for 16 h. After cooling to room temperature, the volatiles were removed under reduced pressure and 1.5 equivalents of NaBARF in 5 mL CH_2Cl_2 was added. Water (5 mL) was added and the mixture was stirred vigorously for 15 min. The organic layer was removed and the aqueous layer was washed with an additional 5 mL CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4) and the volatiles were removed in *vacuo*. The residue was chromatographed using a short silica column and 10 % hexane/CH_2Cl_2 as the eluent to obtain **1c** (43 %). mp. 145.5-146.4 (decompose). ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (8H, s), 7.52 (4H, s), 7.46-7.40 (3H, m), 7.28-7.26 (2H, m), 7.18-7.10 (1H, m), 6.92-6.89 (1H, m), 4.65-4.50 (1H, m), 4.38 (2H, s), 3.78-3.71 (3H, m), 3.39-3.25 (2H, m), 2.87-2.70 (1H, m), 2.30-1.60 (7H, m), 1.56-1.17 (18H, m), 1.17-1.11 (2H, m), 0.95 (6H, d, J = 6.9 Hz), 0.90 (6H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 162.7, 162.0, 161.3, 160.7, 146.4, 142.5, 139.1, 134.8, 134.5, 131.7, 129.1, 129.0 (2 peaks), 128.6, 128.5, 128.3, 126.5, 126.3, 125.1, 124.8, 122.7, 117.9, 117.5, 117.4, 112.1, 70.5, 61.8, 36.2, 31.7, 29.7, 28.6, 24.3, 23.4, 22.7, 14.1. IR (Thin film, cm^{-1}) 3067, 2967, 2916, 2851, 1609, 1458, 1354, 1277, 1161, 1126, 995, 949, 934, 887, 837. HRMS (ESI, TOF): Exact mass calcd for $C_{42}H_{55}IrN_3O$ *ie* $[M]^+$ 810.3974. Found 810.3998 and $C_{32}H_{12}BF_{24}^-$ *ie* $[M]^-$ 863.0654. Found 863.0634.


A-benzi_cat_2
STANDARD 1H OBSERVE
iPr
BARF
1c
a + b + c + d
m
m
l
h
g
e + k + n
f + o
j
f1 (ppm)

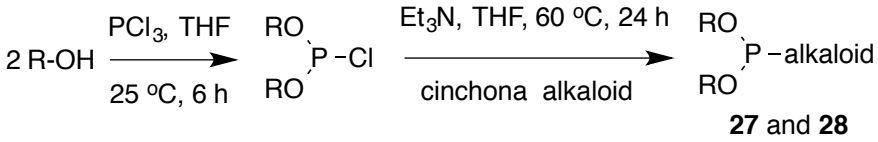

iPr
BARF
1c
a + b + c + d + l
j + k + n + o
i
p
m
h
e + g
f
f1 (ppm)

B. Catalytic Hydrogenation Conditions

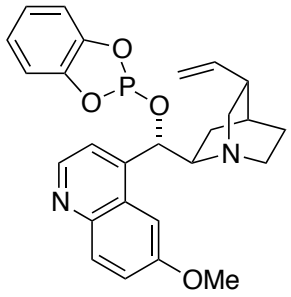
The corresponding alkenes (0.25 mmol) and Ir-catalyst (1-2 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 10 - 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

APPENDIX E
EXPERIMENTAL FOR CHAPTER V

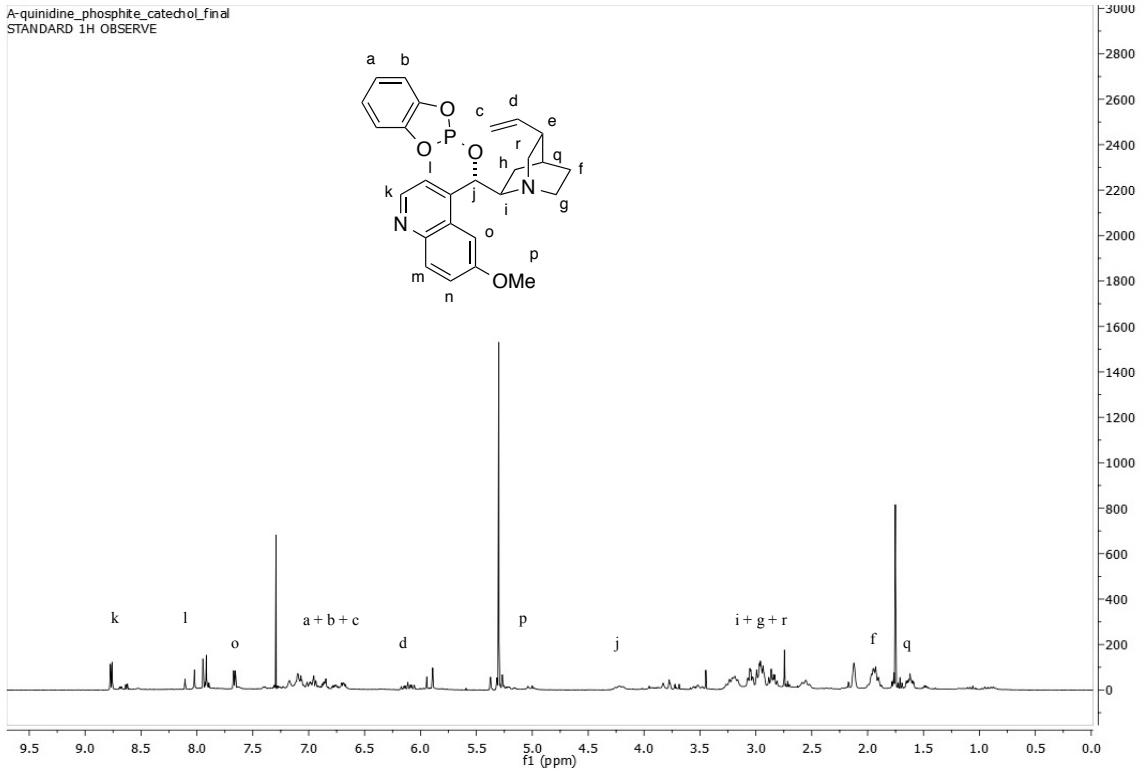
A. General Procedure for Preparation of Compounds 27 and 28.[201]

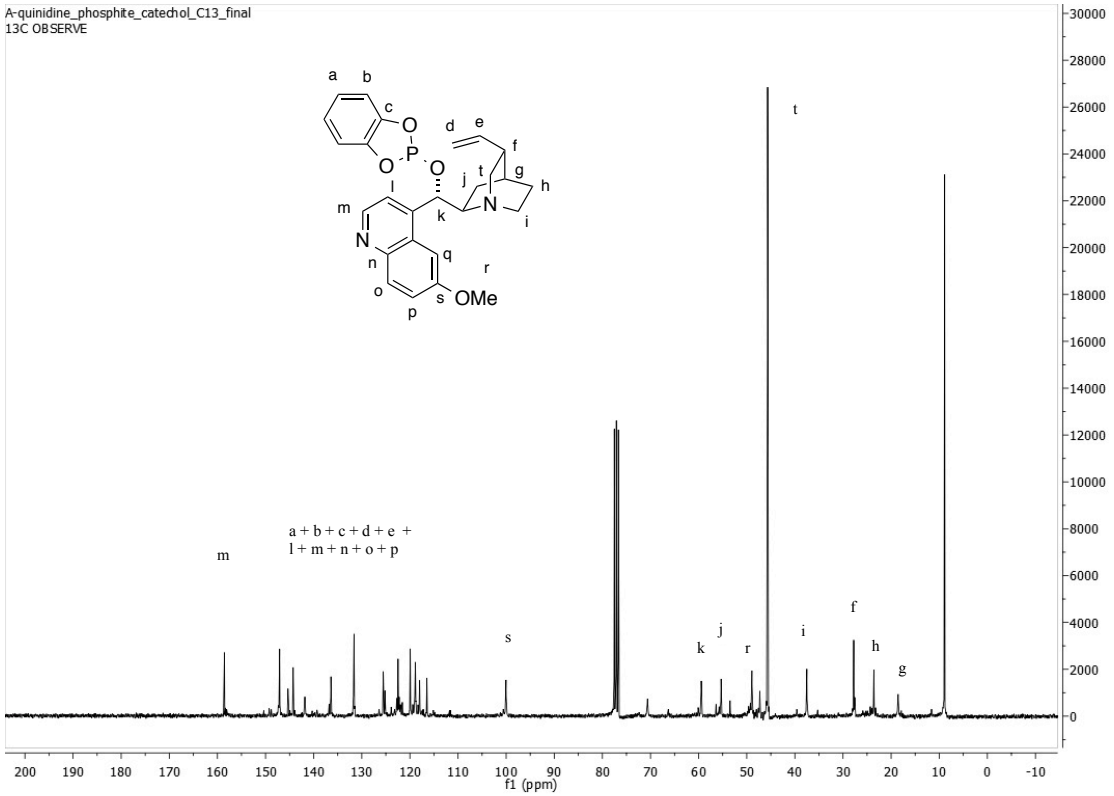


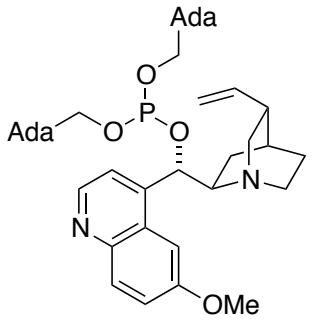
A solution of appropriate alcohol (2 equiv) or diol (1 equiv) in THF was added dropwise to phosphorus trichloride (0.42 g, 3 mmol) under nitrogen. The mixture was stirred at room temperature until completion (TLC). Subsequently, selected cinchona alkaloids (3 mmol) were added to the mixture followed by triethylamine (3 mL). The reaction was stirred and heated to 60 °C for 24 h, then the suspension was filtered and the mother liquor was concentrated to give a light yellow solid. This solid was dissolved in water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure to give light yellow crude product. The product purified by flash column chromatography on silica gel using n-hexane/acetone/triethylamine (3:3:1) as the eluent.



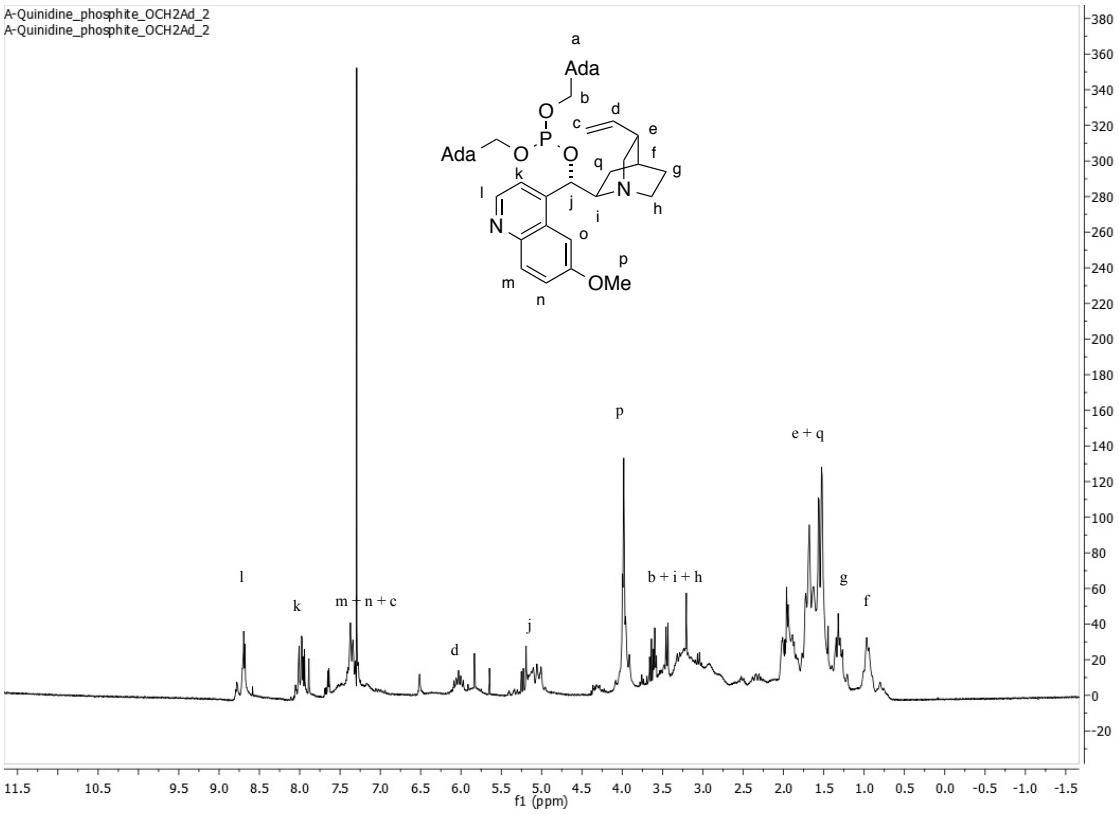
(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-(Benzo[*d*][1,3,2]dioxaphosphol-2-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **27a (**0.85 g, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 4.5 Hz), 7.90 (1H, d, *J* = 9.3 Hz), 7.52 (1H, d, *J* = 4.5 Hz), 7.24 (1H, dd, *J* = 2.4, 6.0 Hz), 7.16 (1H, d, *J* = 2.7 Hz), 6.12-6.00 (2H, m), 5.72 (1H, d, *J* = 3.3 Hz), 5.31 (1H, s), 5.10-5.08 (1H, m), 5.06-5.04 (1H, m), 3.82 (3H, s), 3.54-3.46 (1H, m), 3.08-2.76 (4H, m) 2.27-2.22 (1H, m), 2.16-2.07 (2H, m), 1.77 (1H, b), 1.57-1.47 (1H, m) 1.26 (1H, s), 1.13-1.04 (1H, m), 0.90-0.87 (1H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 147.2, 145.3, 144.3, 141.8, 136.4, 131.7, 125.5, 122.8, 122.5, 122.2, 121.6, 119.9, 118.9, 118.0, 116.5, 100.0, 70.6, 59.4, 55.3, 48.9, 45.8, 37.5, 27.8, 23.6, 18.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 143.5. HRMS (ESI): Exact mass calcd for $C_{26}H_{27}N_2O_4P$ *ie* $[M+H]^+$ 463.1787. Found 463.1762.

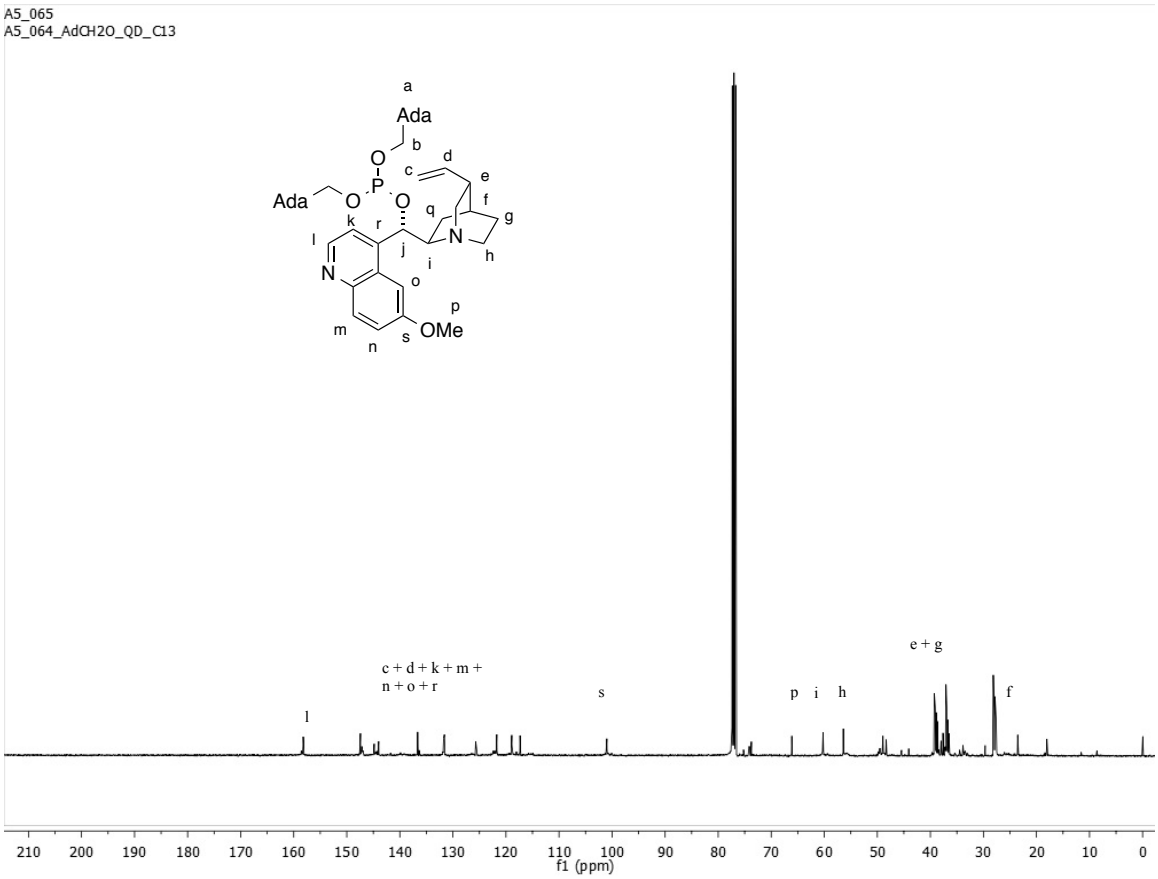

A-quinidine_phosphite_catechol_final
STANDARD 1H OBSERVE
a b
c d e
r q f
h
l
O
P
O
O
j
i
N
g
k
N
o
p
m
n
OMe
k l o a + b + c d p j i + g + r f q
f1 (ppm)

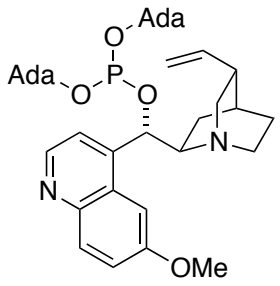

A-quinidine_phosphite_catechol_C13_final
13C OBSERVE
a b
c
d e
f
O
P
O
O
l
j t
g
h
m
k
N
i
N
n
q
r
o
p
s
OMe
t
a + b + c + d + e +
l + m + n + o + p
m
s
k
j
r
i
f
h
g
f1 (ppm)



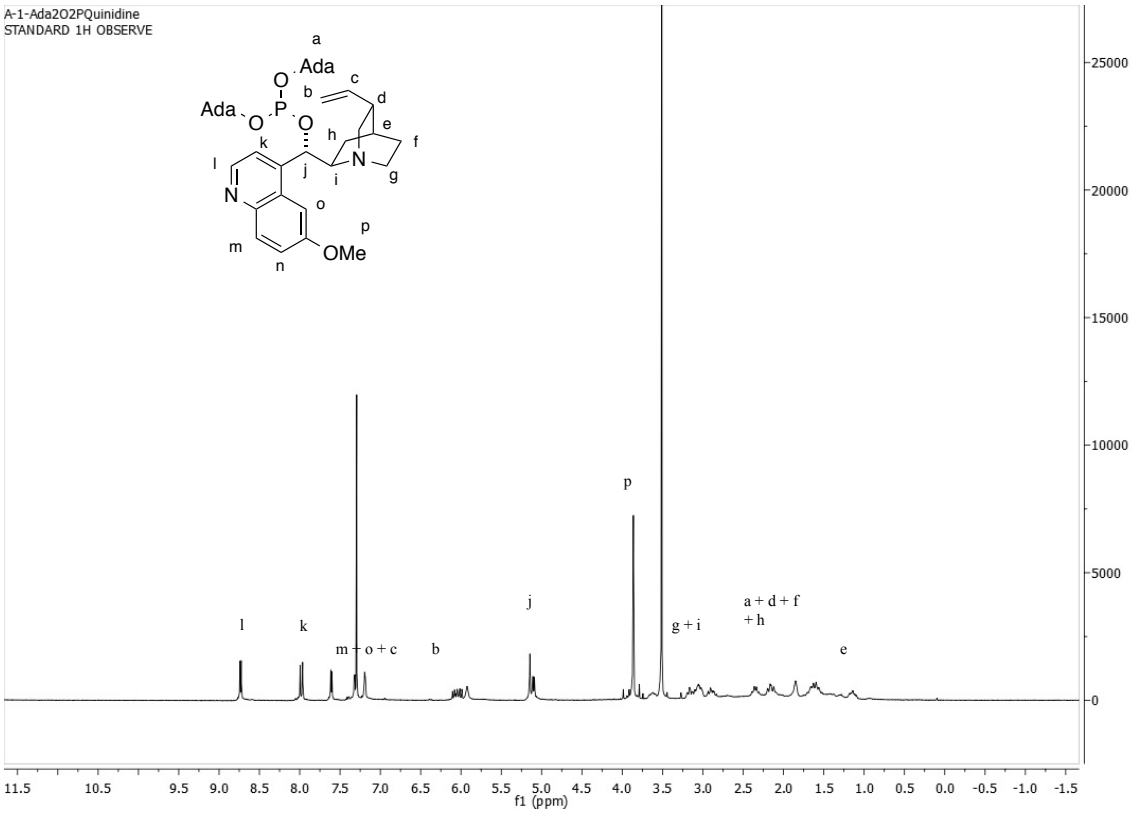
bis(Adamantan-1-ylmethyl) ((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) phosphite; **27b** (0.5 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 4.5 Hz), 7.90 (1H, d, *J* = 9.3 Hz), 7.52 (1H, d, *J* = 4.5 Hz), 7.24 (1H, dd, *J* = 2.4, 6.0 Hz), 7.16 (1H, d, *J* = 2.7 Hz), 6.12-6.00 (2H, m), 5.72 (1H, d, *J* = 3.3 Hz), 5.31 (1H, s), 5.10-5.08 (1H, m), 5.06-5.04 (1H, m), 3.82 (3H, s), 3.54-3.46 (1H, m), 3.08-2.76 (4H, m) 2.27-2.22 (1H, m), 2.16-2.07 (2H, m), 1.77 (1H, b), 1.57-1.47 (1H, m) 1.26 (1H, s), 1.13-1.04 (1H, m), 0.90-0.87 (1H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 147.2, 145.3, 144.3, 141.8, 136.4, 131.7, 125.5, 122.8, 122.5, 122.2, 121.6, 119.9, 118.9, 118.0, 116.5, 100.0, 70.6, 59.4, 55.3, 48.9, 45.8, 37.5, 27.8, 23.6, 18.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 145.2. HRMS (ESI): Exact mass calcd for $C_{42}H_{57}N_2O_4P$ *ie* $[M+H]^+$ 685.4134. Found 685.4198.

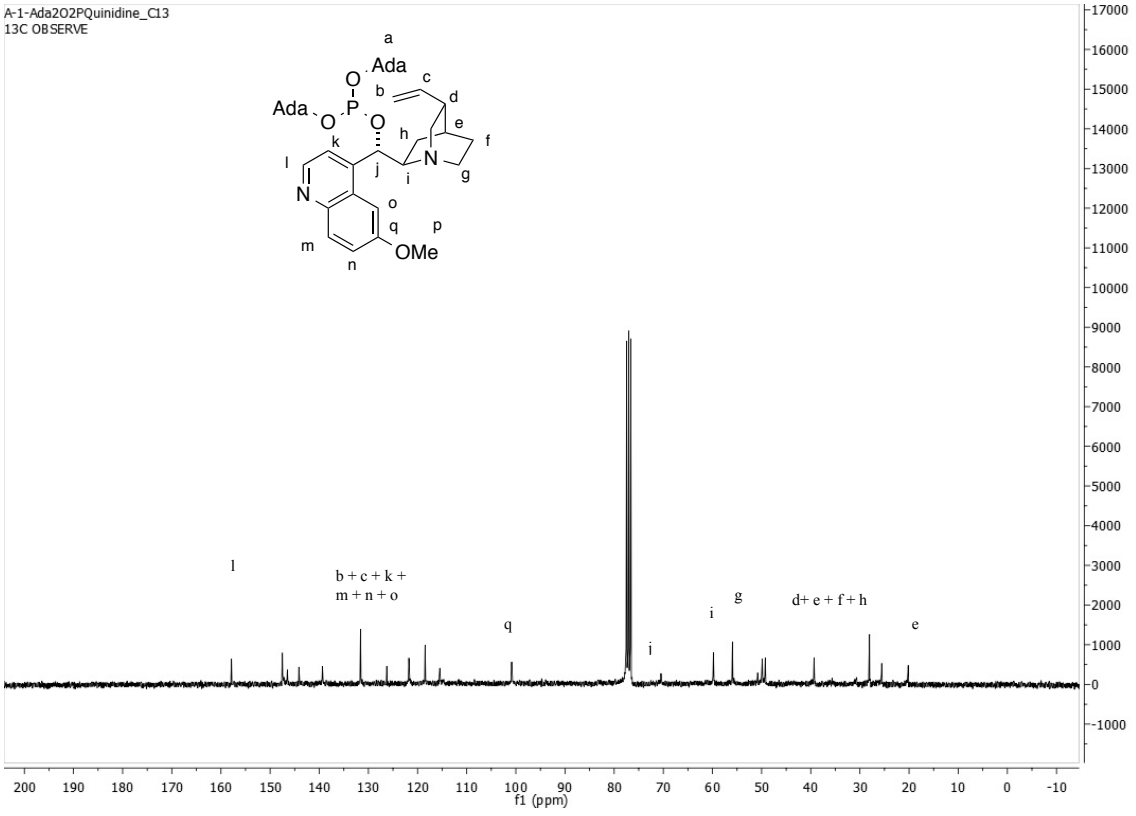

A-Quinidine_phosphite_OCH2Ad_2
A-Quinidine_phosphite_OCH2Ad_2
Ada
OMe
l
k
m + n + c
d
j
p
b + i + h
e + q
g
f
f1 (ppm)

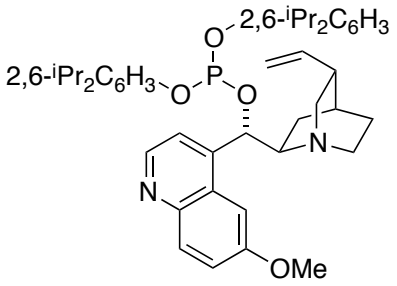

A5_065
A5_064_AdCH2O_QD_C13
Ada
OMe
l
c + d + k + m + n + o + r
s
p i h
e + g
f
f1 (ppm)



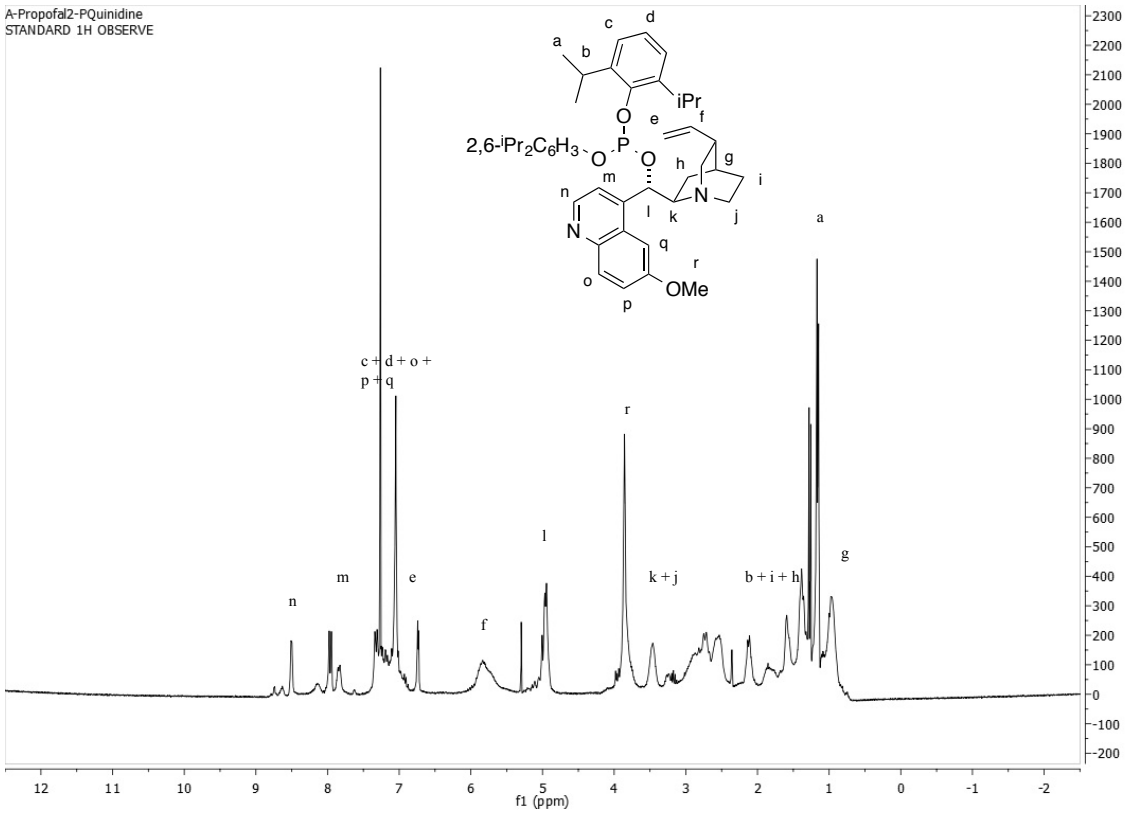
bis(Adamantan-1-yl) ((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) phosphite; **27c** (0.6 g, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (1H, d, J = 4.5 Hz), 7.98 (1H, d, J = 9.3 Hz), 7.61 (1H, d, J = 4.5 Hz), 7.33-7.29 (1H, m), 7.20-7.19 (1H, m), 6.06 (1H, dd, J = 9.6, 12.9 Hz), 5.99-5.92 (1H, b), 5.14 (2H, s), 5.12-5.08 (1H, m), 3.86 (3H, s), 3.64-3.59 (1H, m), 3.51, (10H, b), 3.17-3.00 (6H, m), 2.94-2.86 (4H, m), 2.39-2.30 (4H, m), 2.20-2.08 (3H, m) 2.19-1.84 (4H, m), 1.71-1.09 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.6, 146.5, 144.1, 139.4, 131.7, 126.3, 121.7, 118.5, 115.5, 100.9, 70.5, 70.4, 59.7, 55.9, 50.8, 49.8, 49.2, 39.3, 280, 27.9, 25.5, 20.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 140.8. HRMS (ESI): Exact mass calcd for $C_{40}H_{53}N_2O_4P$ *ie* $[M+H]^+$ 657.3821. Found 657.3797.

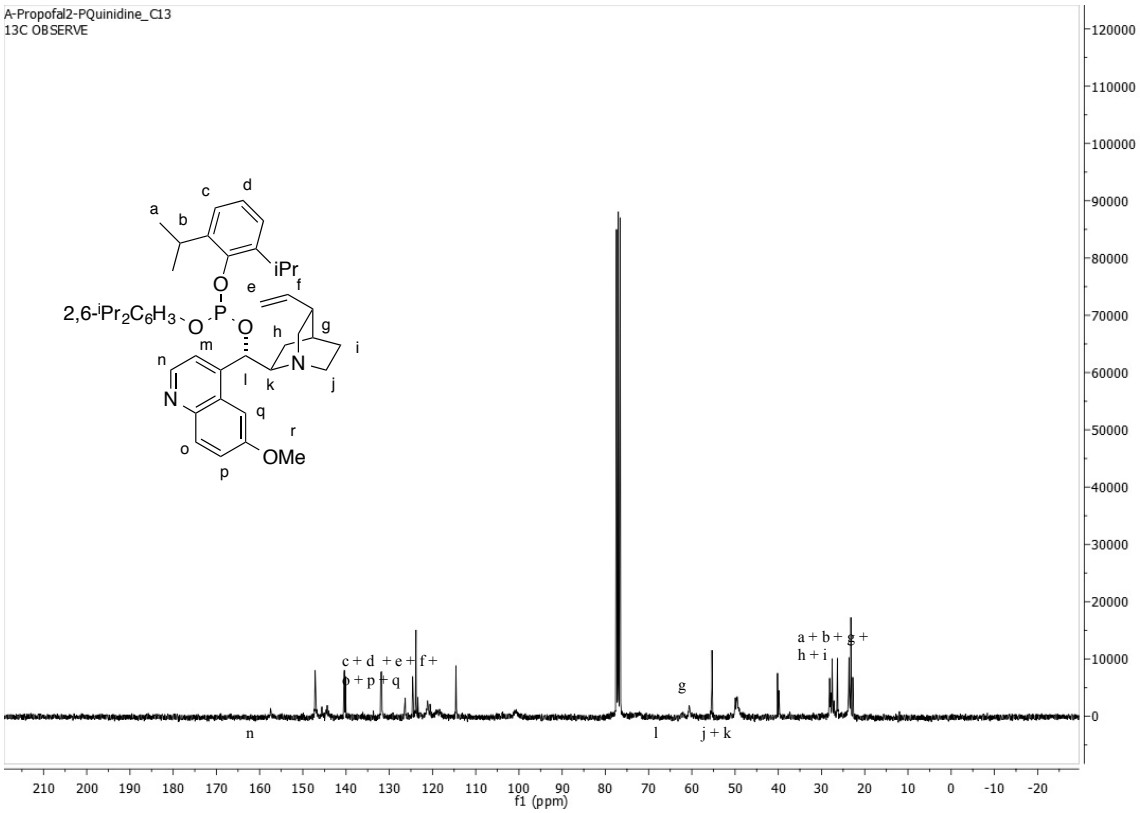

A-1-Ada2O2PQuinidine
STANDARD 1H OBSERVE
Ada
OMe
l
k
m + o + c
b
j
p
g + i
a + d + f + h
e
f1 (ppm)

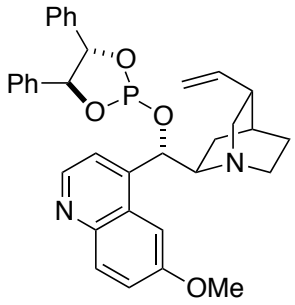

A-1-Ada2O2PQuinidine_C13
13C OBSERVE
Ada
OMe
l
b + c + k + m + n + o
q
i
g
d+ e + f + h
e
f1 (ppm)



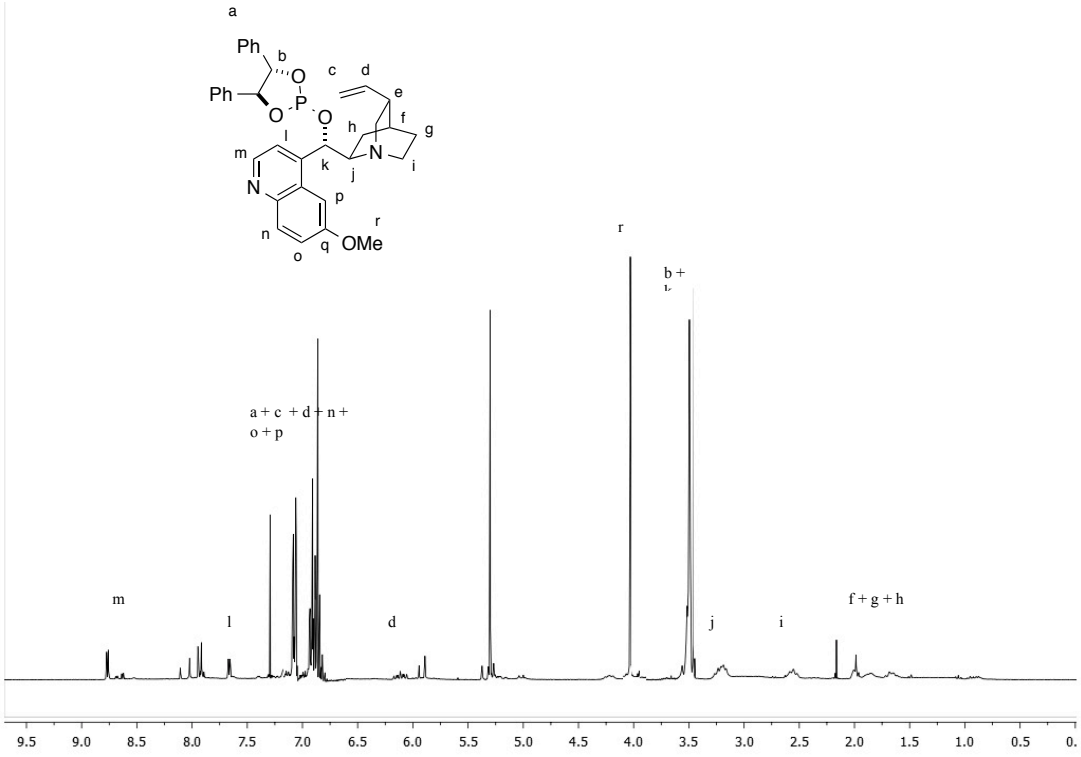
bis(2,6-Diisopropylphenyl)-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) phosphite; **27d** (0.6 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51-8.50 (1H, m), 8.15-8.13 (1H, m), 8.02-7.95 (2H, m), 7.33-7.29 (1H, m), 7.85-7.82 (1H, m), 7.42-6.97 (5H, m), 6.74-6.73 (1H, m), 5.93-5.69 (2H, m), 5.11-4.92 (4H, m), 3.48-3.142 (2H, m), 3.27-3.15 (1H, m), 2.97-2.46, (10H, m), 2.14-2.07 (2H, m), 1.59-1.55 (3H, m), 1.45-1.32 (3H, m), 1.29-1.26 (6H, m) 1.17-1.15 (6H, m), 1.00-0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 147.3, 147.2, 147.0, 146.9, 144.4, 140.5, 140.1, 133.6, 131.9 (2 peaks), 131.8, 126.3, 124.6, 123.8, 123.4, 121.2 (2 peaks), 121.1 (2 peaks), 120.6, 114.6, 101.0, 55.3, 50.0, 49.9, 49.7 (2 peaks), 49.6, 49.4, 49.3, 40.2, 39.9, 28.1, 28.0, 27.9, 27.5, 27.1, 26.3, 23.8, 23.6, 23.4, 23.1, 22.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 143.5. HRMS (ESI): Exact mass calcd for $C_{44}H_{57}N_2O_4P$ *ie* $[M+H]^+$ 709.4134. Found 709.4202.

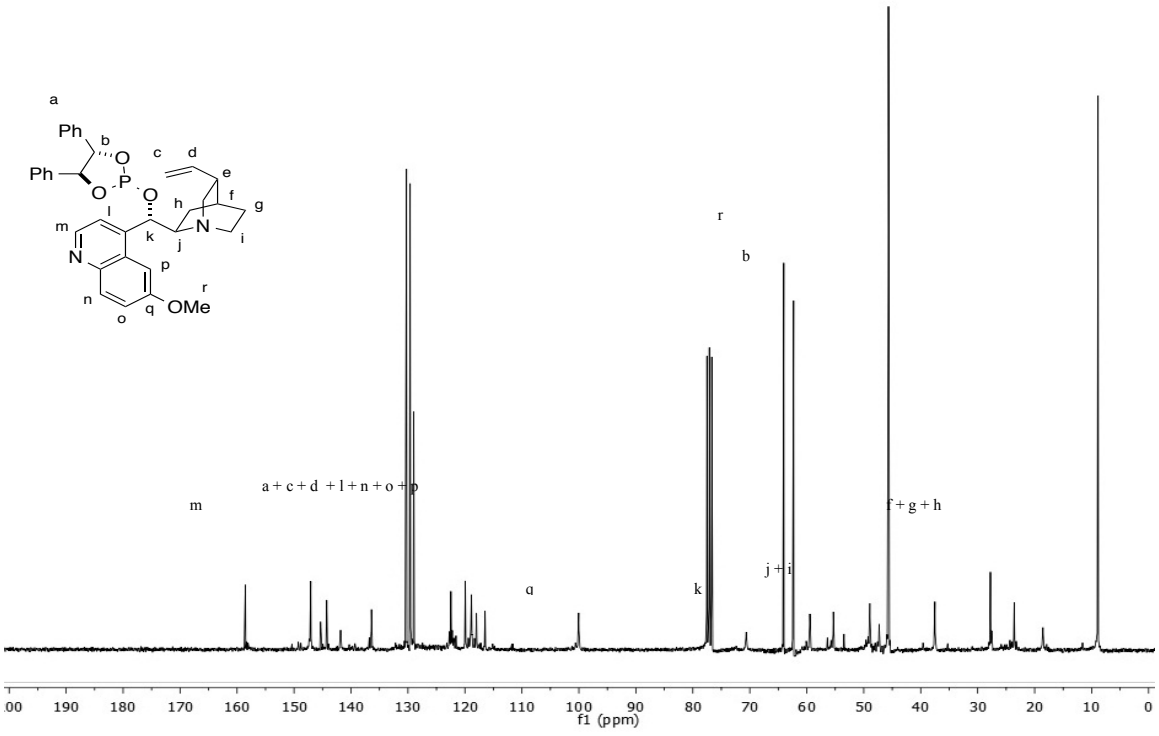

A-Propofal2-PQuinidine
STANDARD 1H OBSERVE
2,6-iPr2C6H3
iPr
OMe
c + d + o + p + q
r
l
a
m
e
n
f
k + j
b + i + h
g
f1 (ppm)

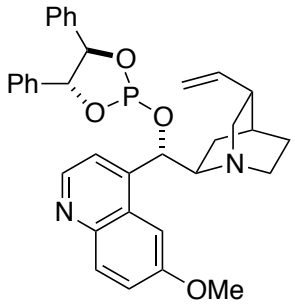

A-Propofal2-PQuinidine_C13
13C OBSERVE
2,6-iPr2C6H3
iPr
OMe
c + d + e + f + o + p + q
n
g
l
j + k
a + b + g + h + i
f1 (ppm)



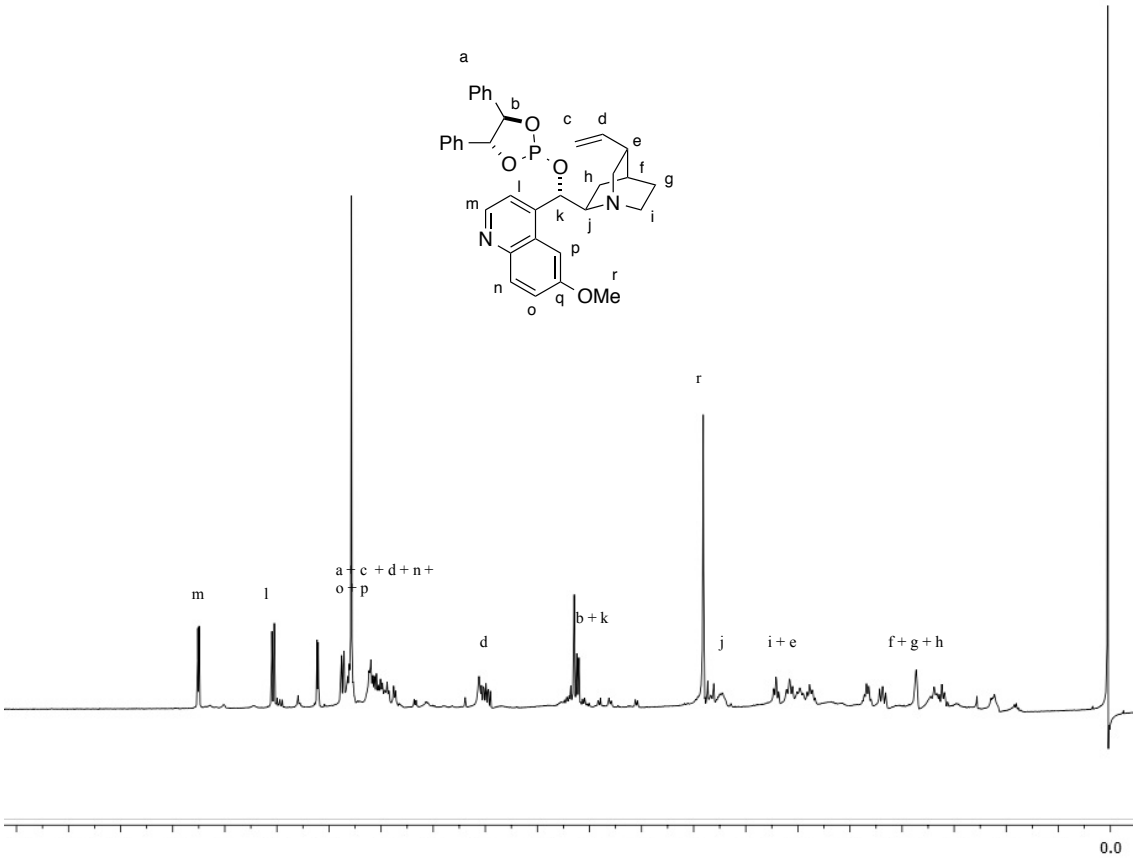
(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-(((4*S*,5*S*)-4,5-Diphenyl-1,3,2-dioxaphospholan-2-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **27e** (0.3 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, *J* = 4.4 Hz), 7.92 (1H, d, *J* = 9.3 Hz), 7.50 (1H, d, *J* = 4.5 Hz), 7.15-7.03 (5H, m), 6.95-6.76 (7H, m), 6.18-6.05 (2H, m), 5.80 (1H, d, *J* = 3.3 Hz), 5.31 (1H, s), 5.10-5.02 (2H, m), 4.02 (3H, s), 3.62-3.47 (4H, m), 3.28-3.15 (2H, m) 2.27-2.22 (1H, m), 2.10-2.03 (2H, m), 1.73-1.68 (1H, m), 0.90-0.87 (1H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 147.0, 145.1, 144.3, 141.0, 135.9, 131.8 (2 peaks), 130.2 (2 peaks), 129.7, 125.4, 122.8, 122.6, 122.2, 120.2, 119.3, 118.5, 117.9, 117.0, 100.1, 70.6, 64.8, 63.4, 59.4, 55.3, 48.3, 45.8, 37.3, 27.8, 23.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 144.1. HRMS (ESI): Exact mass calcd for $C_{34}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 567.2413. Found 567.2467.

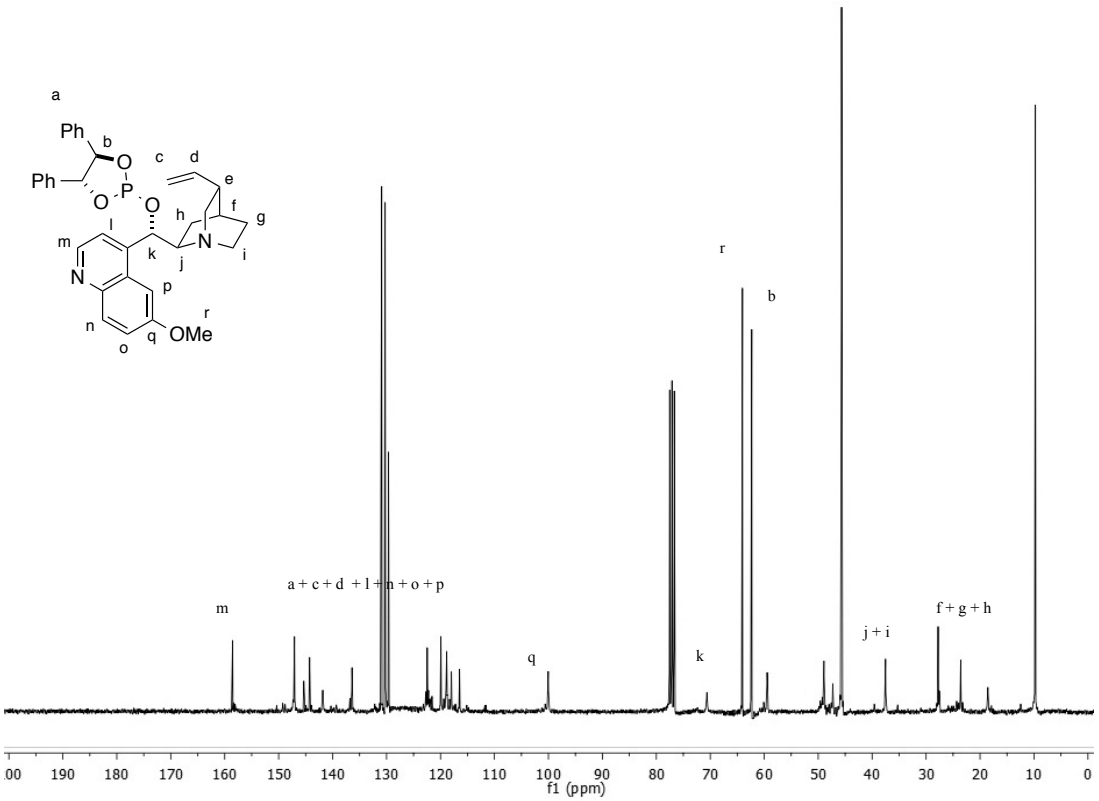

a
Ph
b
O
c
d
Ph
O
P
O
e
O
h
f
g
l
m
k
N
i
j
N
p
r
n
q
OMe
o
r
b +
a + c + d + n +
o + p
m
l
d
j
i
f + g + h
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

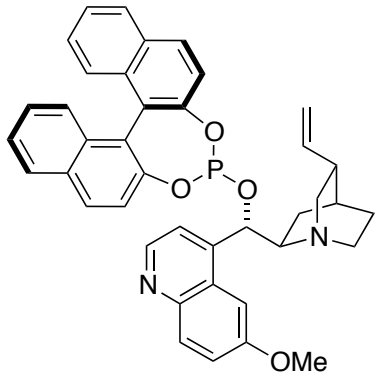

a
Ph
b
O
c
d
Ph
O
P
O
e
O
h
f
g
l
m
k
N
i
j
N
p
r
n
q
OMe
o
r
b
a + c + d + l + n + o + p
m
q
k
j + i
f + g + h
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



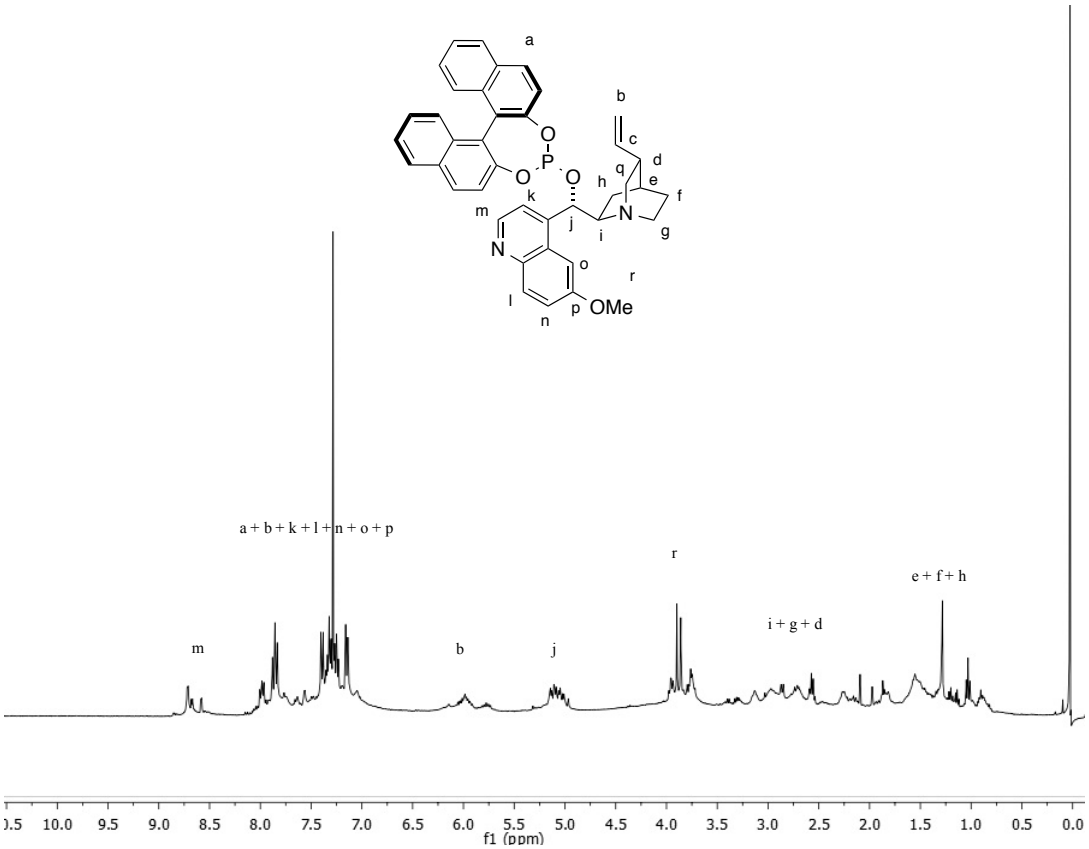
(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-(((4*R*,5*R*)-4,5-Diphenyl-1,3,2-dioxaphospholan-2-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **27f** (0.4 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (1H, d, *J* = 4.5 Hz), 8.03 (1H, d, *J* = 9.2 Hz), 7.61 (1H, d, *J* = 4.5 Hz), 7.38-7.30 (5H, m), 7.11-6.94 (6H, m), 6.06-5.95 (2H, m), 5.15 (1H, s), 5.11 (2H, d, *J* = 8 Hz), 3.91 (3H, s), 3.86-3.70 (1H, m), 3.27-2.85 (5H, m) 2.34-2.31 (1H, m), 2.22-2.16 (1H, m), 1.86 (1H, m), 1.69-1.59 (2H, m), 1.12-1.10 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 148.2, 145.4, 144.8, 141.7, 136.5, 130.8 (2 peaks), 130.2 (2 peaks), 129.5, 124.5, 122.8, 122.6, 122.3, 120.1, 119.5, 118.1, 117.0, 100.0, 71.2, 64.5, 63.7, 59.5, 49.0, 47.5, 46.0, 37.8, 27.8, 18.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 144.2. HRMS (ESI): Exact mass calcd for $C_{34}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 567.2413 Found 567.2471.

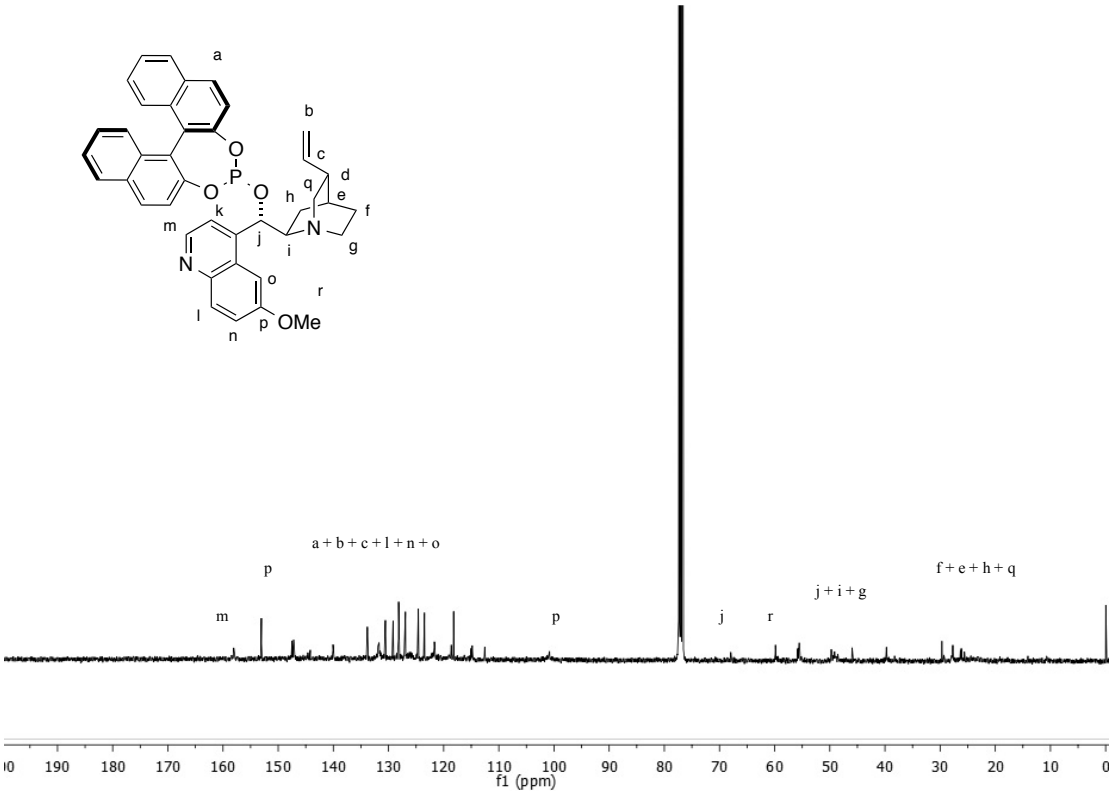

a
Ph
b
O
c
d
Ph
O
P
O
e
f
g
h
l
m
k
N
j
i
N
p
r
n
q
OMe
o
r
m
l
a + c + d + n +
o + p
d
b + k
j
i + e
f + g + h
0.0

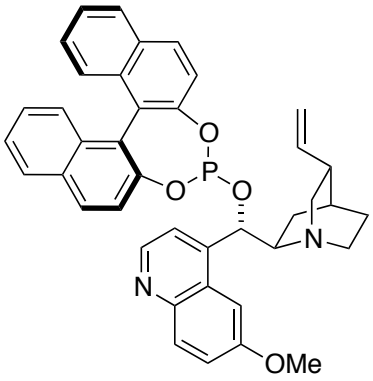

a
Ph
b
O
c
d
Ph
O
P
O
e
f
g
h
l
m
k
N
j
i
N
p
r
n
q
OMe
o
r
b
m
a + c + d + l + n + o + p
q
k
j + i
f + g + h
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



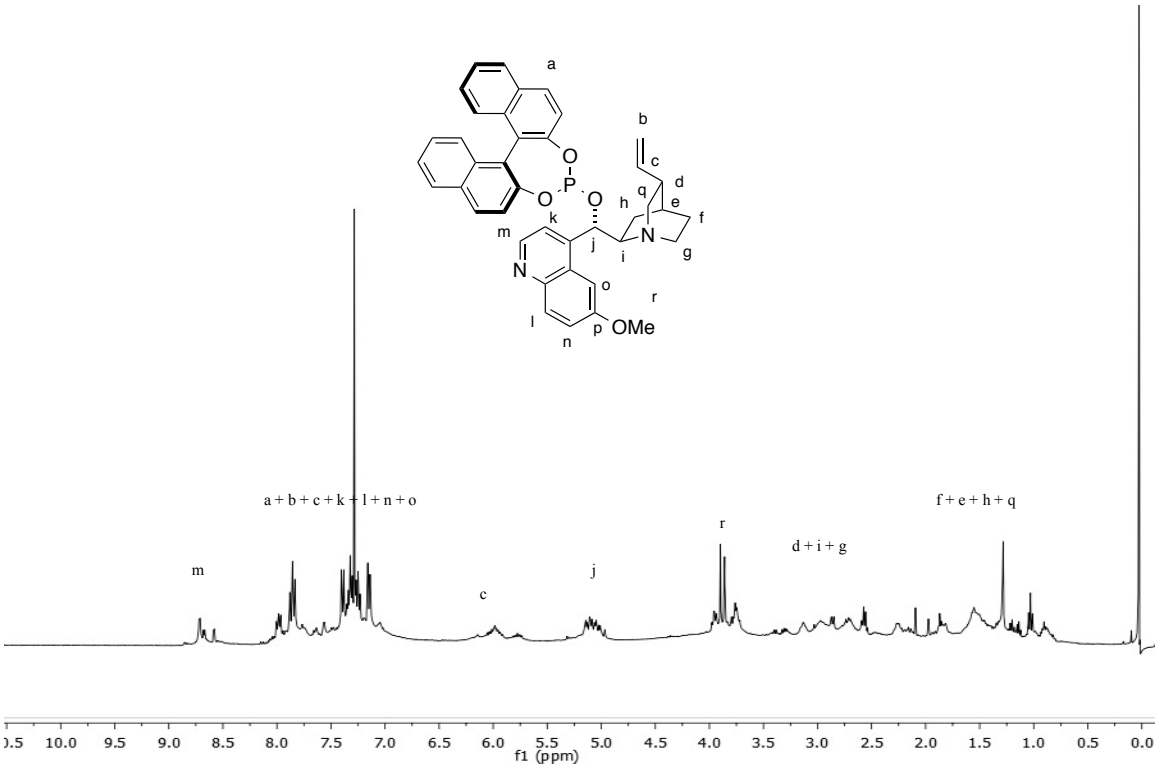
(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-(Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **27g** (0.5 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (1H, d, *J* = 4.5 Hz), 8.05 (1H, d, *J* = 9.3 Hz), 7.96-7.78 (2H, m), 7.70-7.51 (4H, m), 7.51-7.03 (9H, m), 6.24-6.06 (2H, m), 5.85-5.70 (1H, m), 5.29 (1H, s), 3.98 (3H, s), 3.25-3.16 (1H, m) 2.90-2.53 (2H, m), 2.05-1.90 (1H, m), 1.81-1.75 (1H, m), 1.52-1.27 (3H, m), 0.92-0.85 (3H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 147.9, 145.8, 145.3, 142.1, 135.7, 135.5, 132.7, 132.6, 132.5, 132.4, 132.2, 131.6, 131.5 (2 peaks), 131.3, 131.2 (2 peaks), 130.9, 130.7, 130.0, 129.5, 129.1, 128.8, 127.5, 127.3, 123.5, 119.3, 102.1, 80.1, 62.1, 55.8, 52.1, 50.9, 37.3, 27.8, 27.0, 26.1, 12.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6. HRMS (ESI): Exact mass calcd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2477.


a + b + k + l + n + o + p
m
b
j
r
i + g + d
e + f + h
f1 (ppm)

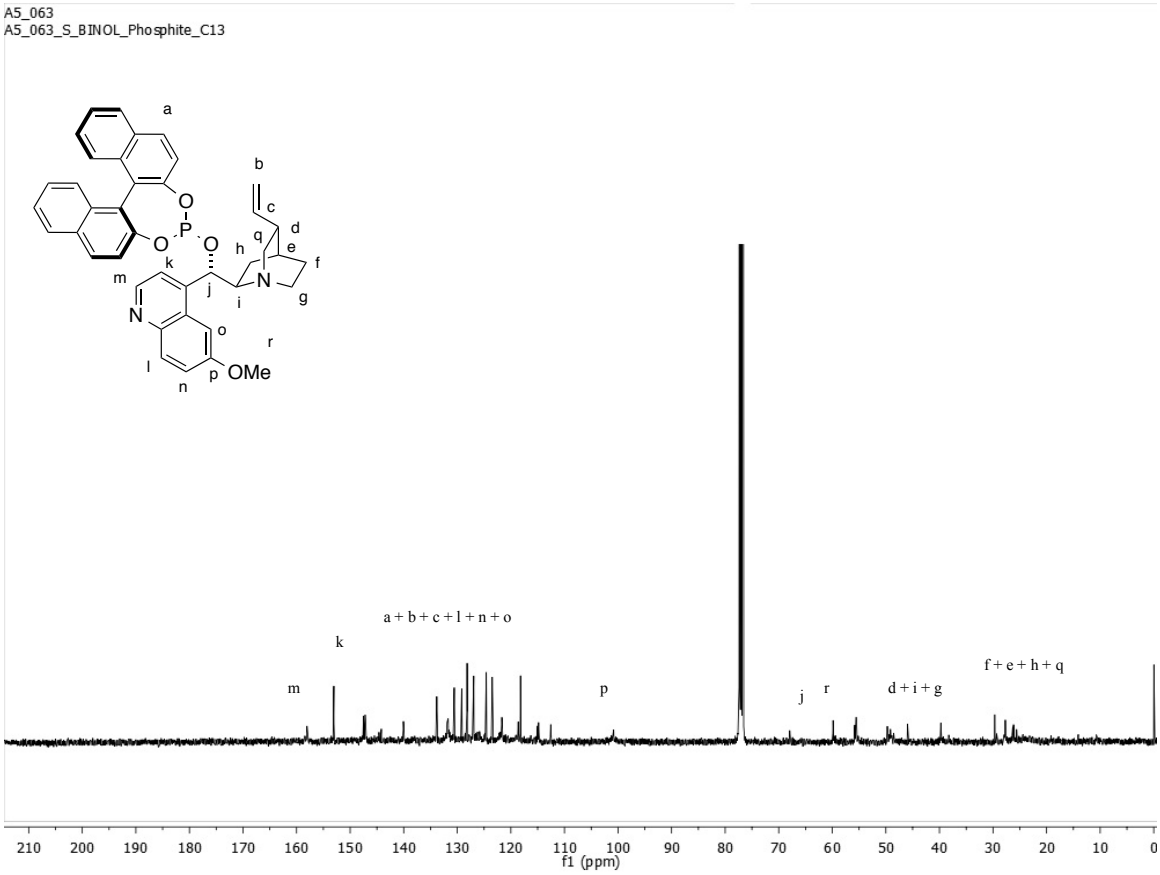

a + b + c + l + n + o
p
m
p
j
r
j + i + g
f + e + h + q
f1 (ppm)

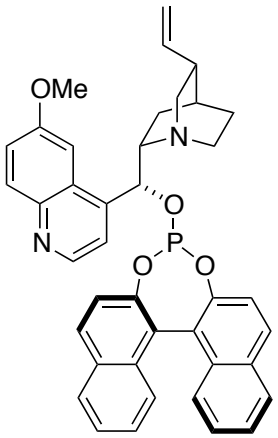


(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-((11b*S*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **27h** (0.5 g,35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, d, *J* = 4.5 Hz), 8.10 (1H, d, *J* = 9.3 Hz), 8.05-7.82 (2H, m), 7.78-7.70 (4H, m), 7.65-7.08 (9H, m), 6.32-6.25 (2H, m), 5.80-5.70 (1H, m), 5.29 (1H, s), 3.96 (3H, s), 3.28-3.19 (1H, m), 2.92-2.53 (2H, m), 2.05-1.90 (1H, m), 1.78-1.75 (1H, m), 1.51-1.27 (3H, m), 0.92-0.85 (3H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 153.0, 147.5, 147.2, 147.1, 144.6, 144.2, 140.1, 139.9, 133.8, 131.9, 131.8, 131.7, 130.6, 129.2, 128.5, 128.2, 126.9, 126.0, 125.8, 124.6, 123.5, 121.7, 121.0, 118.7, 118.2, 115.0, 114.8, 112.6, 100.8, 679, 59.8, 55.8, 55.6, 55.5, 49.7, 49.1, 48.5, 46.0, 39.7, 39.6, 29.7, 27.9, 27.7, 27.6, 26.3, 26.2, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6. HRMS (ESI): Exact mass calcd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2437.

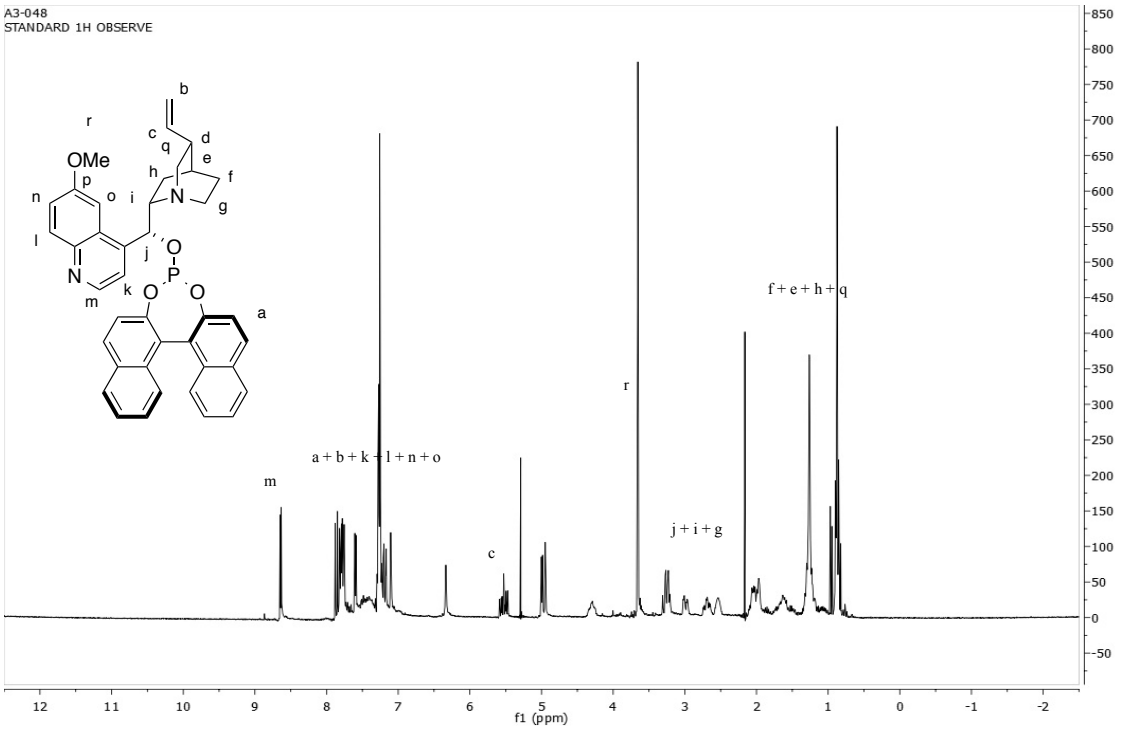


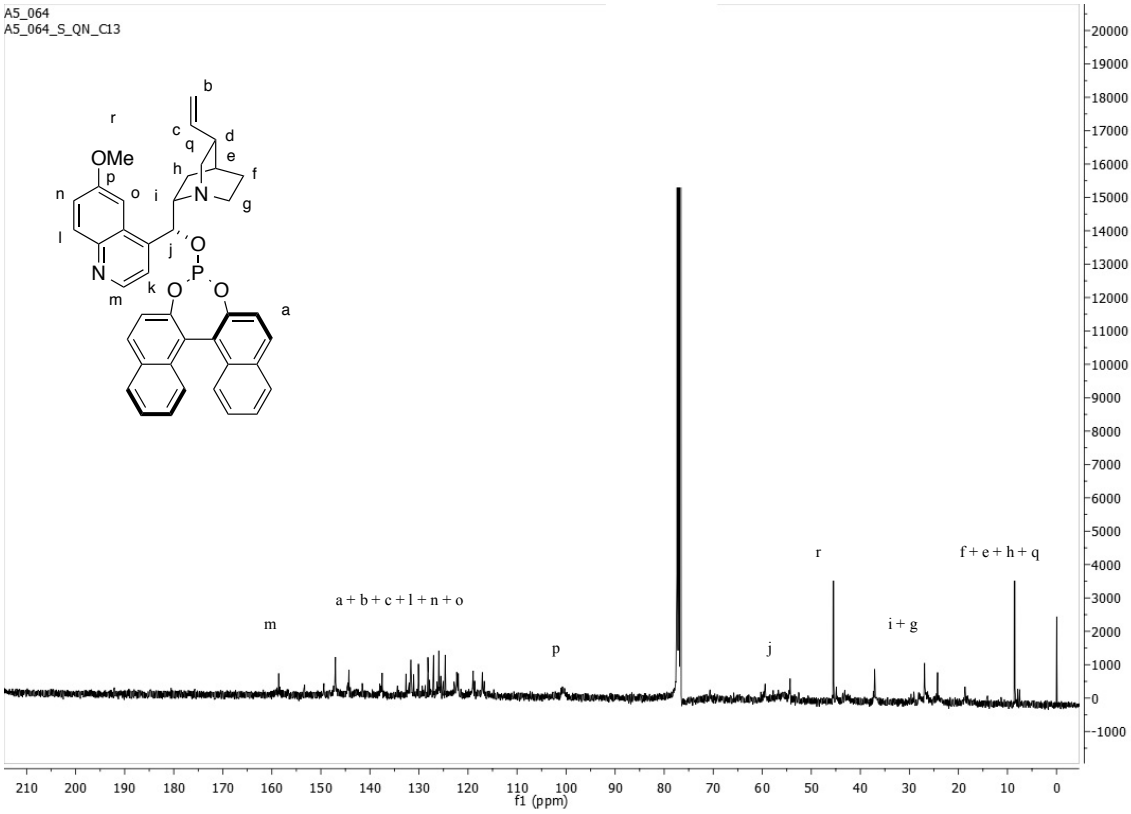
A5_063
A5_063_S_BINOL_Phosphite_C13

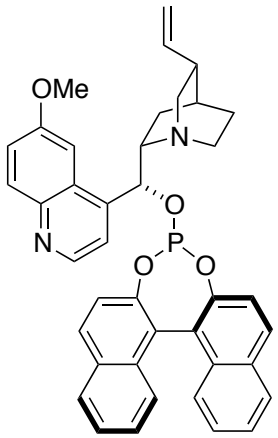




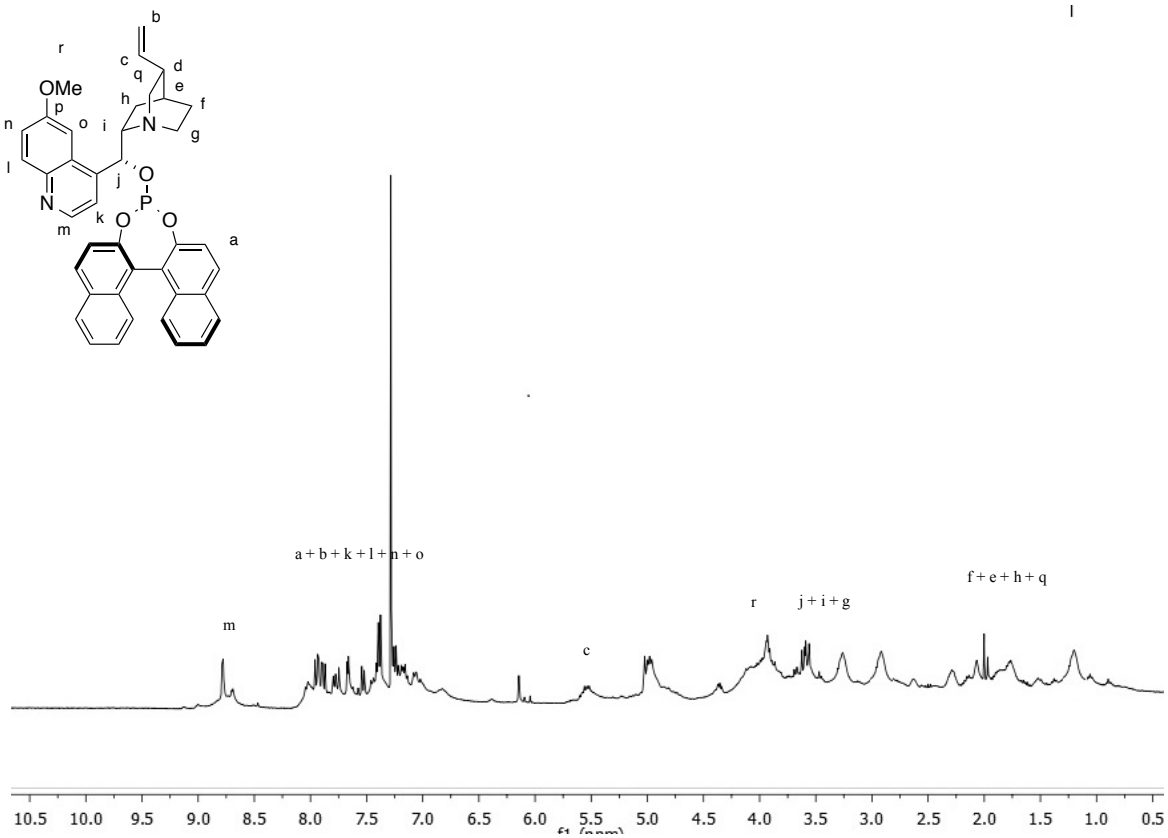
(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11b*R*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **28g** (0.4 g, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (1H, d, *J* = 4.5 Hz), 7.97-7.80 (5H, m), 7.53 (2H, d, *J* = 3.3 Hz), 7.48-7.40 (1H, m), 7.29-7.04 (8H, m), 6.45-6.40 (2H, m), 5.65-5.48 (1H, m), 5.03 (1H, d, *J* = 3.6 Hz), 4.98 (1H, s), 4.38-4.30 (1H, m), 3.63(3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.75-2.50 (1H, m), 2.04-1.97 (1H, m), 1.77-1.46 (1H, m), 1.32-1.15 (2H, m), 0.92-0.85 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (2 peaks), 132.4 (2 peaks), 132.2, 131.8 (2 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, 123.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7. HRMS (ESI): Exact mass calcd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2437.

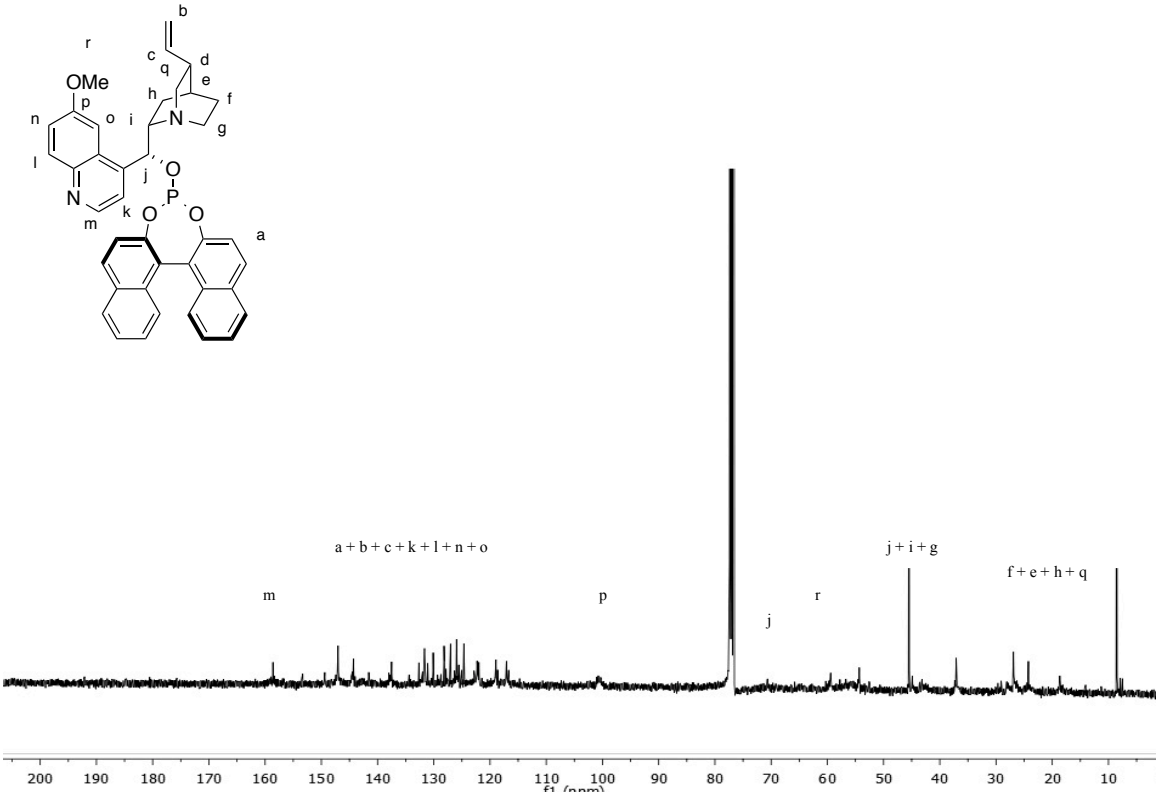

A3-048
STANDARD 1H OBSERVE
OMe
a + b + k + l + n + o
m
c
r
j + i + g
f + e + h + q
f1 (ppm)


A5_064
A5_064_S_QN_C13
OMe
a + b + c + l + n + o
m
p
j
r
i + g
f + e + h + q
f1 (ppm)



(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11b*S*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **28h** (0.3 g, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (1H, d, *J* = 4.8 Hz), 8.05-7.87 (5H, m), 7.80-7.66 (2H, m), 7.54-7.52 (1H, m), 7.42-7.16 (8H, m), 6.95-6.79 (2H, m), 5.60-5.49 (1H, m), 5.03-4.95 (1H, m), 4.41-4.37 (1H, m), 4.33-3.56 (4H, m), 3.30-3.23 (1H, m), 2.65-2.64 (1H, m), 2.31-1.78 (5H, m), 1.55-1.01(3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 152.3, 149.5, 149.4, 147.0, 144.3, 141.6, 141.5, 138.0 (2 peaks), 137.8, 137.7, 137.5, 134.4, 132.6, 131.7, 131.6, 131.1, 130.1, 128.2, 127.8, 127.0, 125.9 (2 peaks), 125.5, 125.0, 124.6, 122.8, 122.3 (2 peaks), 122.2 (2 peaks), 122.1, 122.0 (2 peaks), 118.9 (2 peaks), 59.4, 54.3, 37.1, 26.8, 24.2, 18.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7. HRMS (ESI): Exact mass calcd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2437.

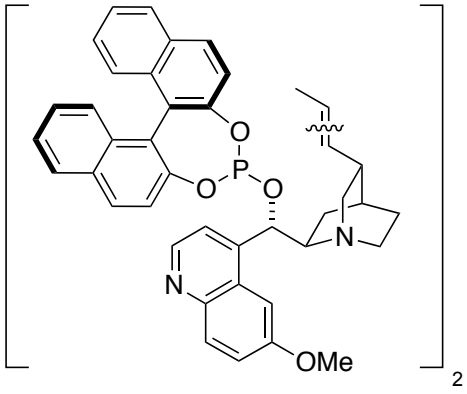

OMe
N
O
P
a + b + k + l + n + o
m
c
r
j + i + g
f + e + h + q
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5


OMe
N
O
P
a + b + c + k + l + n + o
m
p
j
r
j + i + g
f + e + h + q
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

B. General Procedure for Metathesis of Cinchona Alkaloid Ligands.

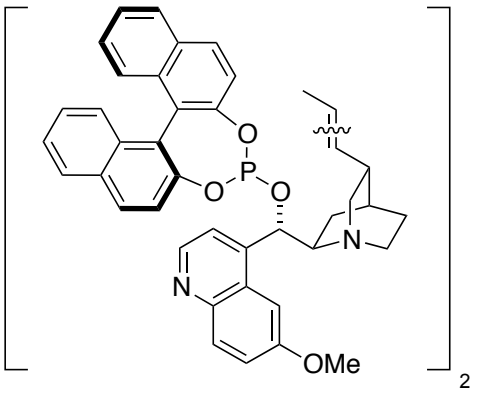
Appropriate cinchona alkaloid was added to 2nd Generation Hoveyda-Grubb's catalyst (5 mol %) in CH_2Cl_2 in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 ^oC for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent was removed under reduced pressure and the crude metathesis was used in the next step without further purification.

The following purification was used only for characterized the homodimer to check the disappearance of monomer starting material. The product was purified by flash column chromatography on silica gel using n-hexane/CH_2Cl_2/triethylamine (6:3:1) as the eluent.

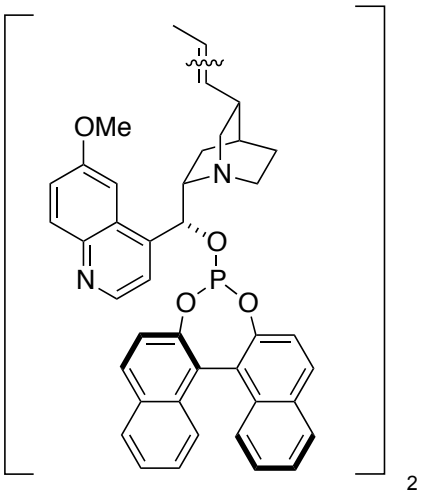


(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-(Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **27g' – 27g'**. 35 % isolated yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J* = 4.5 Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J* = 3.3 Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J* = 3.6 Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H,

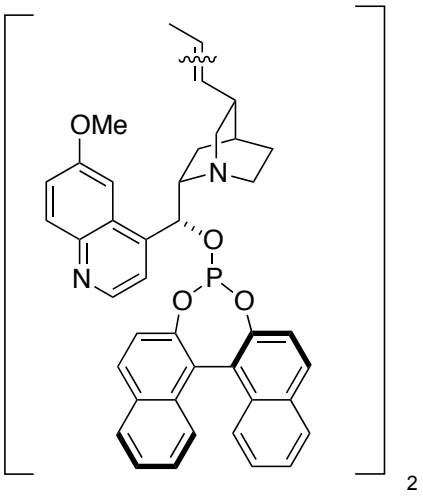
m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (2 peaks), 132.4 (2 peaks), 132.2, 131.8 (2 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, 123.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6.



(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **27h' – 27h'**. 31 % isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, J = 4.5 Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, J = 3.3 Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, J = 3.6 Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (2 peaks), 132.4 (2 peaks), 132.2, 131.8 (2 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, 123.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6.

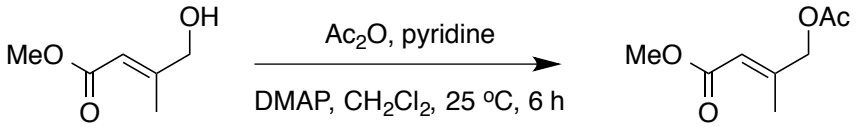


(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11b*R*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **28g' – 28g'**. 40 % isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J* = 4.5 Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J* = 3.3 Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J* = 3.6 Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6, 132.4, 132.2, 131.8, 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, 123.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.8, 12.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7.



(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **28h' – 28h'**. 35 % isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J* = 4.5 Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J* = 3.3 Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J* = 3.6 Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (3 peaks), 132.4 (2 peaks), 132.2, 131.8 (3 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, 123.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7.

C. Preparation of (*E*)-Methyl 4-Acetoxy-3-methylbut-2-enoate, Y.



X **Y**
92 %

To a solution of (*E*)-methyl 4-hydroxy-3-methylbut-2-enoate **X** (1 mmol) and pyridine (3 mmol) in CH_2Cl_2 (7 mL), Ac_2O (1.5 mmol) was added at room temperature and the mixture was stirred until completion (TLC). After completion, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water (15 mL), brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography using 30% EtOAc/hexane to yield (92 %) product **Y** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, s), 4.30 (2H, s), 3.85 (3H, s), 2.08 (3H, s), 1.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.8, 165.2, 126.9, 54.8, 23.6, 16.8. HRMS (ESI): Exact mass calcd for $C_8H_{12}O_4$ *ie* $[M+H]^+$ 173.0814. Found 173.0881.

D. General Procedure for Hydrogenation Using Metathesis Catalysts

For monodentate ligand;

2nd Generation Hoveyda-Grubb's catalyst (0.3 mol %, same amount as use in study reaction) and **1g** was dissolved in CH_2Cl_2 (0.5 M). The mixture was stirred for 15 min, then alkene (0.25 mmol) was added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent.

For bidentate ligand;

2nd Generation Hoveyda-Grubb's catalyst (0.3 mol %, same amount as use in study reaction) and **1g** was dissolved in CH_2Cl_2 (0.5 M) in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 ^oC for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent and other volatile compounds were removed under reduced pressure. The residue was used for the next step without further purification.

New CH_2Cl_2 (0.5 M) was added to the residue, then alkene (0.25 mmol) was added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent.

E. General Procedure for Hydrogenation Using Ir Catalysts

Condition A (for ester substrates);

For monodentate ligand study;

$Ir(COD)_2BARF$ (3 mol %) and appropriate monodentate ligand (6.6 mol %) was dissolved in CH_2Cl_2 (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated ester (0.25 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

For bidentate ligand study;

Appropriate cinchona alkaloid was added to 2nd Generation Hoveyda-Grubb's catalyst (5 mol % based on cinchona alkaloid) in CH_2Cl_2 in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 ^oC for 12 h. Ar (balloon) was

changed every 4 - 6 h. Solvent and other volatile compounds were removed under reduced pressure. The residue was used for the next step without further purification.

$Ir(COD)_2BARF$ (3 mol %) and appropriate cinchona alkaloid ligand (from previous step) was dissolved in CH_2Cl_2 (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated ester (0.25 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

Condition B (for acid substrates);

For monodentate ligand study;

$Ir(COD)_2BARF$ or $Rh(COD)_2BARF$ (3 mol %) and appropriate monodentate ligand (6.6 mol %) was dissolved in MeOH (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated acid (0.25 mmol) and Cs_2CO_3 (0.13 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC analysis.

For bidentate ligand study;

Appropriate cinchona alkaloid was added to 2^{nd} Generation Hoveyda-Grubb's catalyst (5 mol % based on cinchona alkaloid) in CH_2Cl_2 in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 ^oC for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent and other volatile compounds were removed under reduced pressure. The residue was used for the next step without further purification.

$Ir(COD)_2BARF$ or $Rh(COD)_2BARF$ (3 mol %) and appropriate cinchona alkaloid ligand (from previous step) was dissolved in MeOH (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated acid (0.25 mmol) and Cs_2CO_3 (0.13 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC analysis.

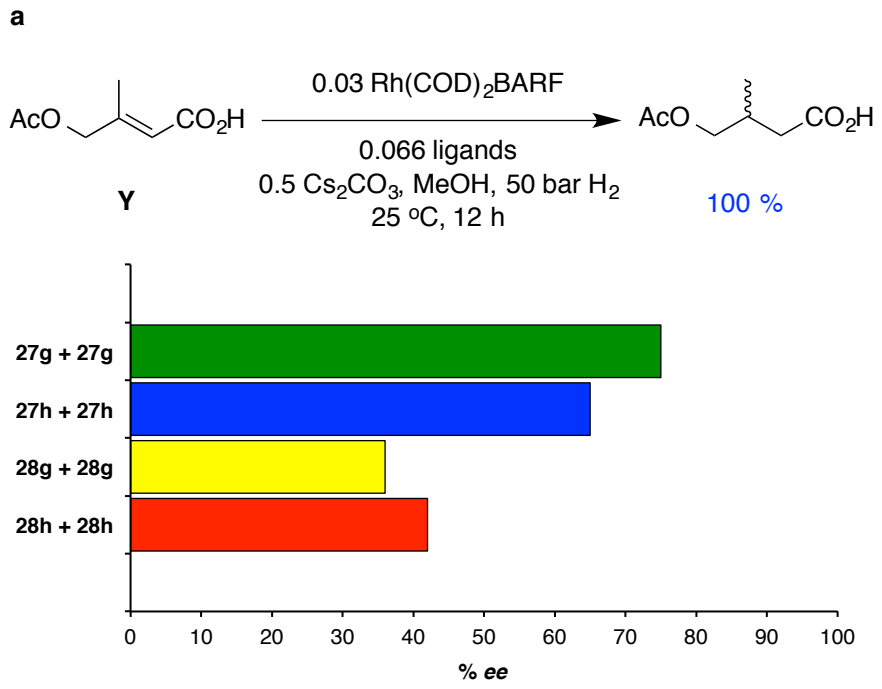


Figure E1. Hydrogenation of the acetoxy acid **Y** using: **a** Rh catalysts from the monodentate ligands **27g**, **27h**, **28g**, and **28h**; and **b** from the same ligands after metathesis (as in Figure 5.9).

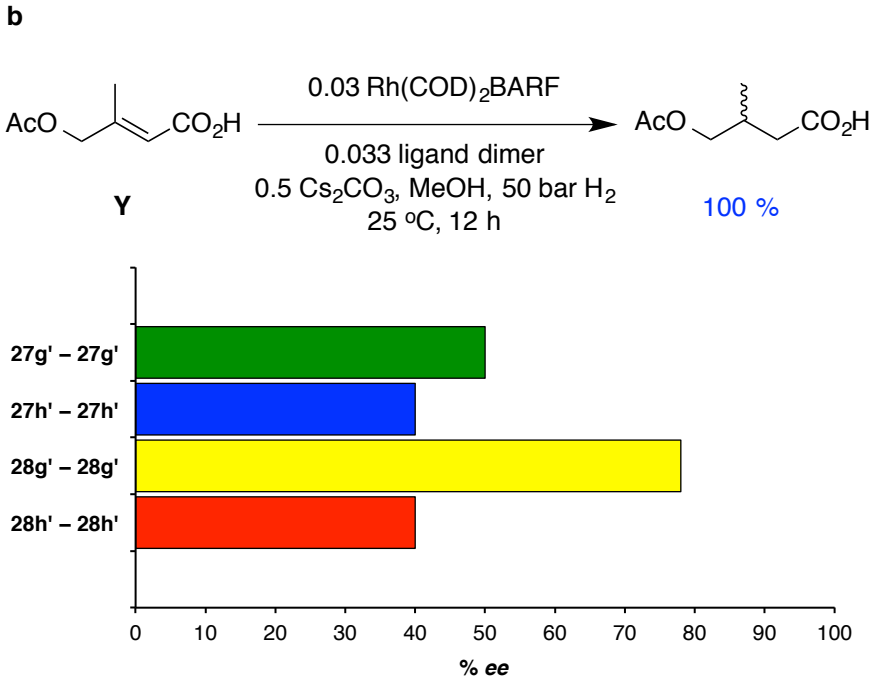


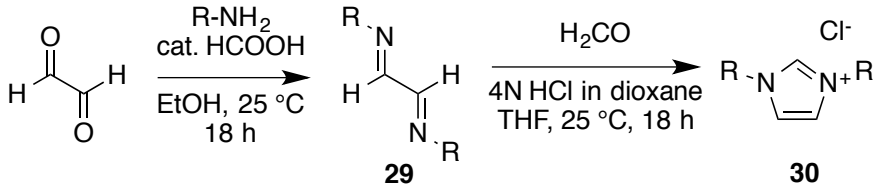
Figure E1. continued

APPENDIX F

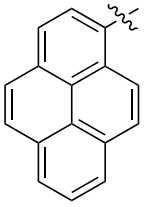
EXPERIMENTAL FOR CHAPTER VI

A. Preparation of Compounds 30 and 32.

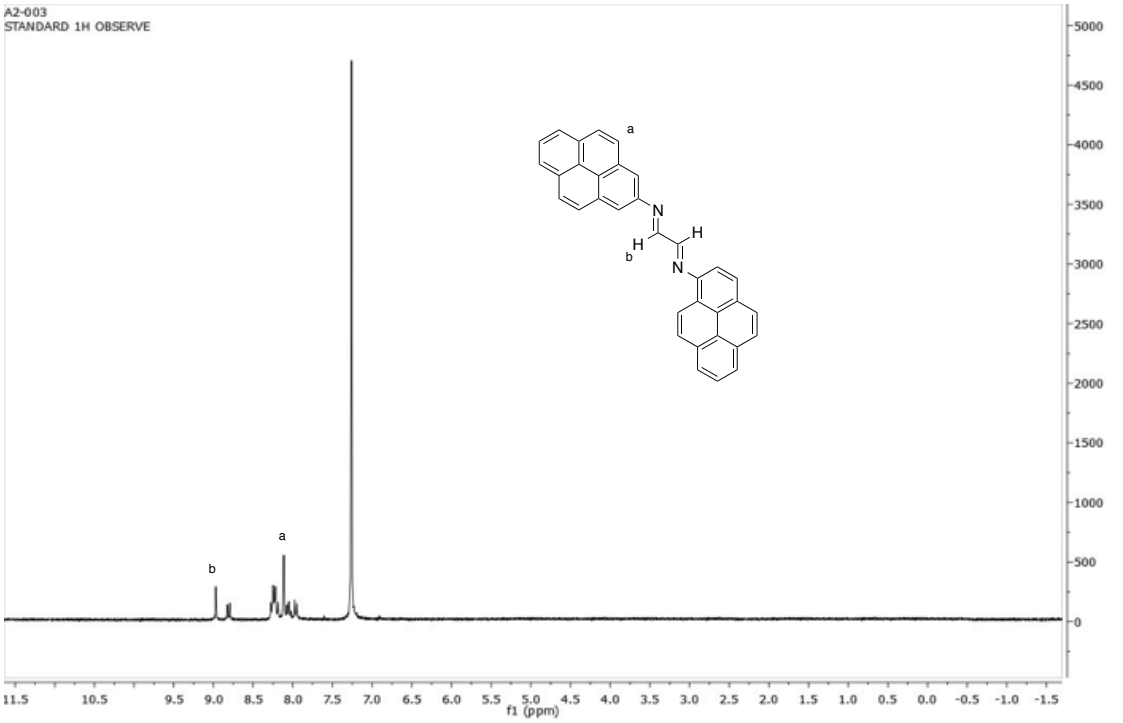
Preparation *N*,*N*'-Di(pyren-1-yl)ethane-1,2-diimine 30.

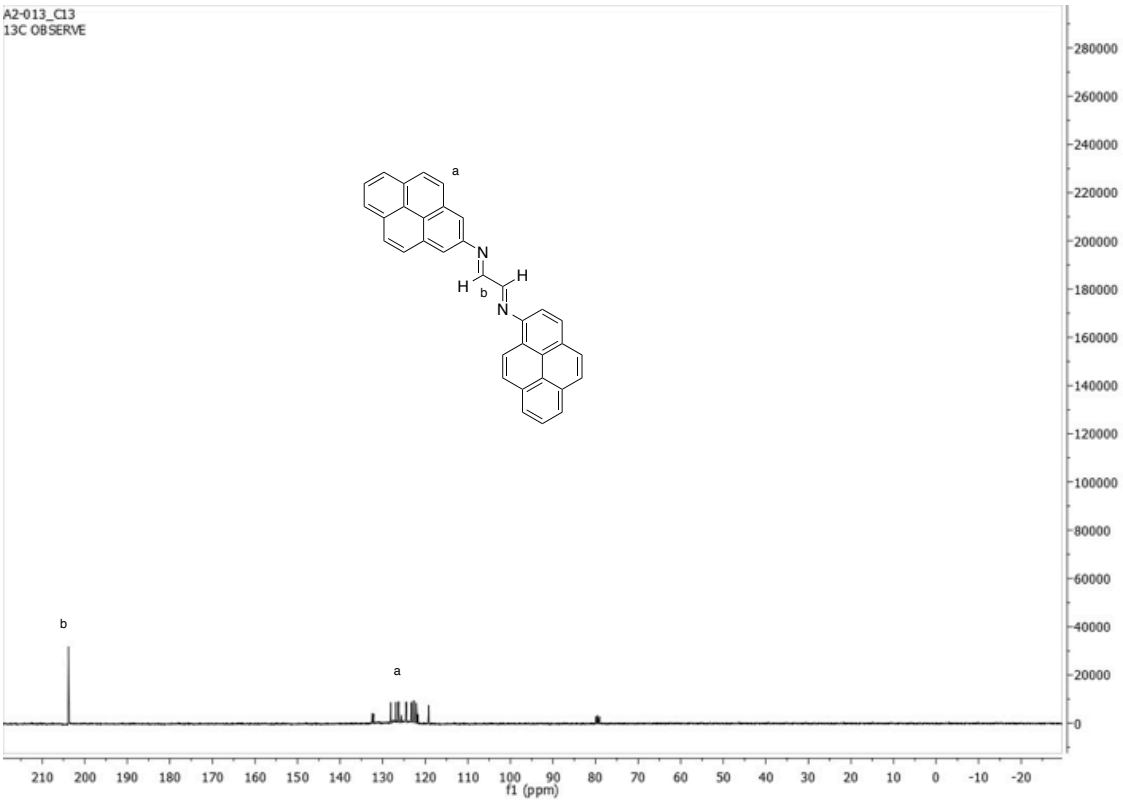


R =



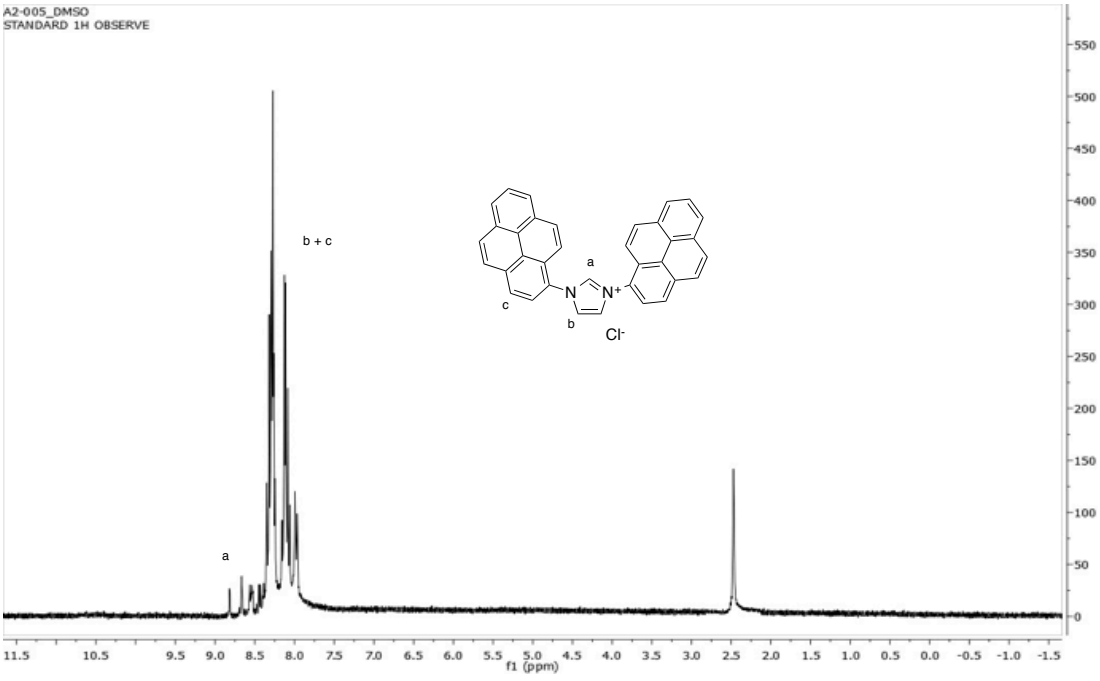
Glyoxal (0.15 mL, 1 mmol) was added to 1-aminopyrene (0.42 g, 2 mmol) in 10 mL of EtOH. The mixture was added catalytic amount of formic acid (0.5 mol %). The mixture was stirred rapidly at room temperature for 18 h to yield red solid. The solid was filtrated and washed with cold EtOH (1 mL) and hexane (10 mL). The product **29** (0.40 g, 0.9 mmol, 88 %) was used with out further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (2H, s), 8.81 (2H, d, J = 9.3 Hz), 8.28-8.18 (8H, m), 8.12-8.11 (4H, m), 8.08-8.02 (2H, m), 7.96 (6H, d, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 132.8, 128.2, 128.0, 127.5, 127.2 (2 peaks), 127.0, 126.5, 126.4 (2 peaks), 126.3, 126.2, 125.3, 125.0, 124.5, 124.3, 121.8, 119.4. MS (ESI): Exact mass calcd for $C_{34}H_{20}N_2$ *ie* $[M+H]^+$ 457.17. Found 457.17.

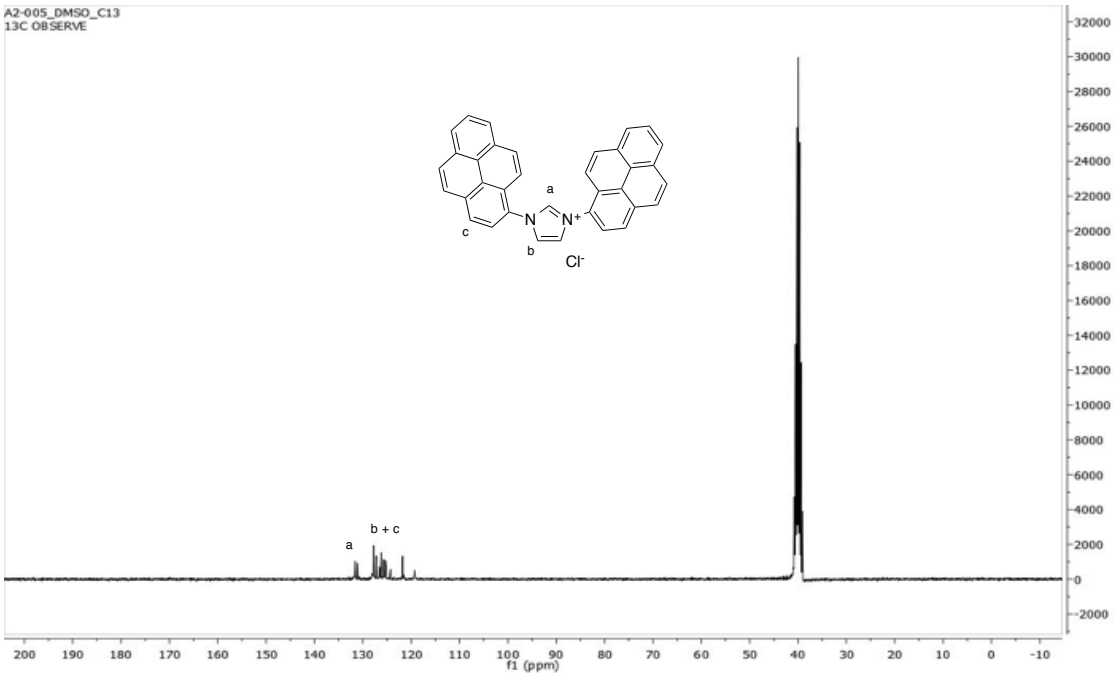

A2-003
STANDARD 1H OBSERVE
a
b
f1 (ppm)

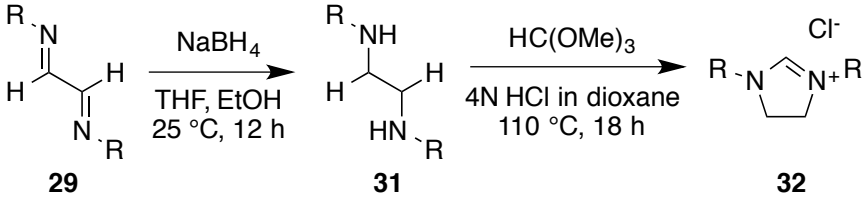

A2-013_C13
13C OBSERVE
a
b
f1 (ppm)

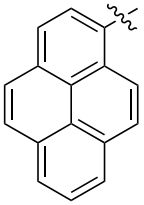
Preparation 1,3-Di(pyren-1-yl)-imidazolium Chloride 30.

To a solution of *N*,*N*'-di(pyren-1-yl)ethane-1,2-diimine **29** (0.40 mL, 0.9 mmol) in THF (10 mL), formaldehyde (0.04 g, 1.3 mmol) and 4N HCl in dioxane (1.5 mL) was added at room temperature. The mixture reaction was stirred rapidly for 18 h. The precipitated solid was filtered and washed with cold THF (3 mL) to give pure desired product **30** (0.38 g, 0.7 mmol, 85 %). ^{1}H NMR (300 MHz, DMSO-*d*6) δ 8.67-8.66 (1H, m), 8.57-8.52 (2H, m), 8.43 (1H, d, *J* = 6.3 Hz), 8.40-8.24 (11H, m), 8.16-8.06 (7H, m), 8.01-7.97 (2H, m); ^{13}C NMR (75 MHz, DMSO-*d*6) δ 131.6 (2 peaks), 131.1, 128.1, 128.0 (3 peaks), 127.9 (3 peaks), 127.8, 127.7 (2 peaks), 127.2, 126.6, 126.5 (2 peaks), 126.3, 126.2, 125.7, 125.3, 125.1, 124.3, 121.8, 119.3. MS (ESI): Exact mass calcd for $C_{35}H_{21}N_2Cl$ *ie* $[M]^+$ 469.16. Found. 469.15.





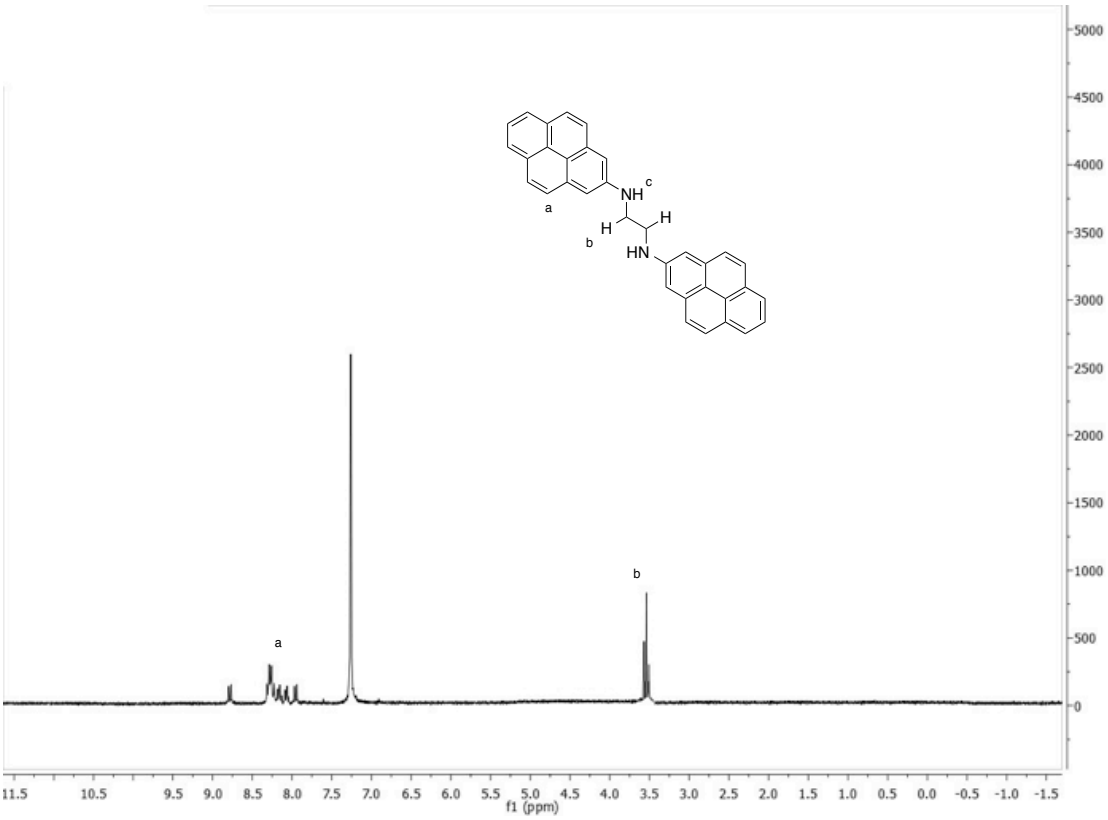


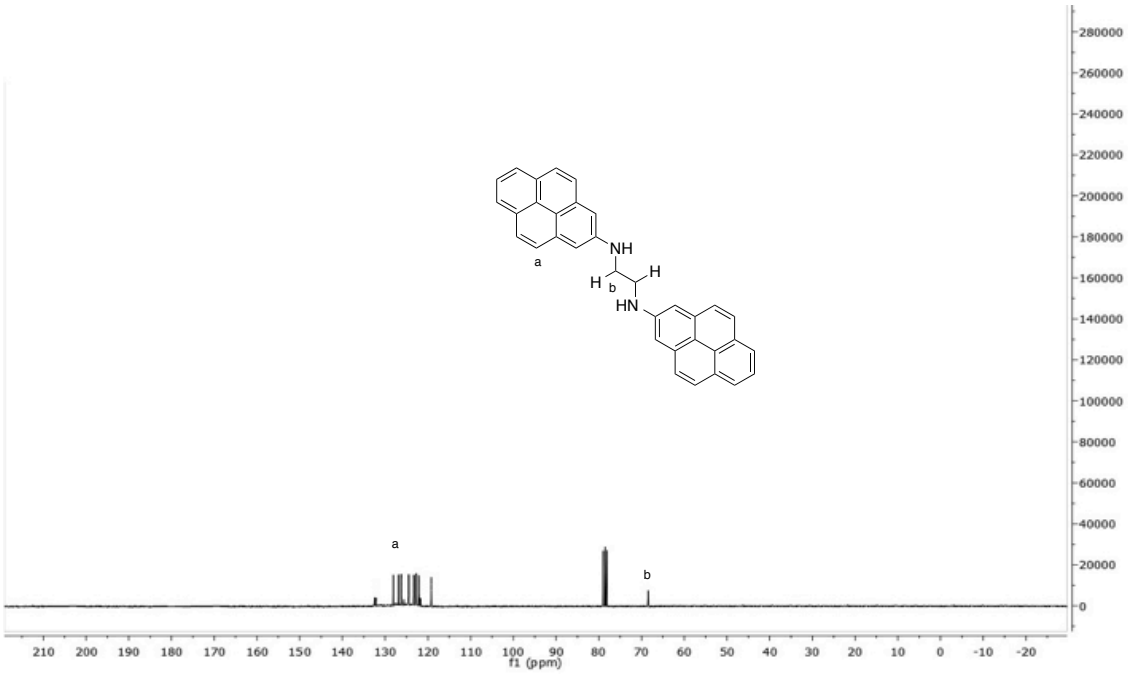
R = 

Preparation *N*,*N*'-Di(pyren-1-yl)ethane-1,2-diamine 31.

N,*N*'-Di(pyren-1-yl)ethane-1,2-diimine **29** (0.22 g, 0.5 mmol) was dissolved in EtOH (15 mL) and THF (10 mL), then $NaBH_4$ (0.08 g, 2mmol) was added to the mixture. After stirred at room temperature for 12 h, the mixture was poured into 1N HCl. The aqueous layer was basified with NaOH then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to yield ethylenediamine product **31** as yellow solid (0.16 g, 0.3 mmol, 60 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (2H, d, J = 9.3 Hz),

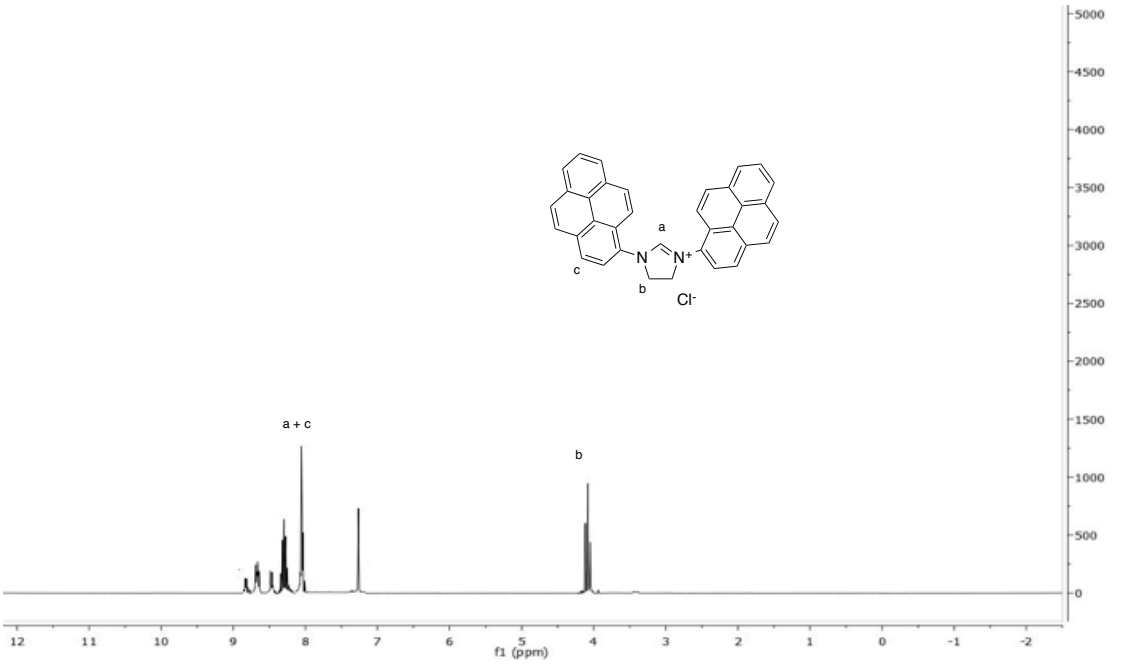
8.25-8.18 (8H, m), 8.12-8.10 (4H, m), 8.08-8.00 (2H, m), 7.95 (6H, d, J = 9.0 Hz), 3.56 (4H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 128.7, 128.4, 127.9, 127.3 (2 peaks), 126.9, 126.7, 126.5 (2 peaks), 126.2, 126.1, 125.6, 125.3, 124.6, 124.3, 121.7, 119.4, 67.3. MS (ESI): Exact mass calcd for $C_{34}H_{24}N_2$ *ie* $[M+H]^+$ 461.20. Found 461.20.

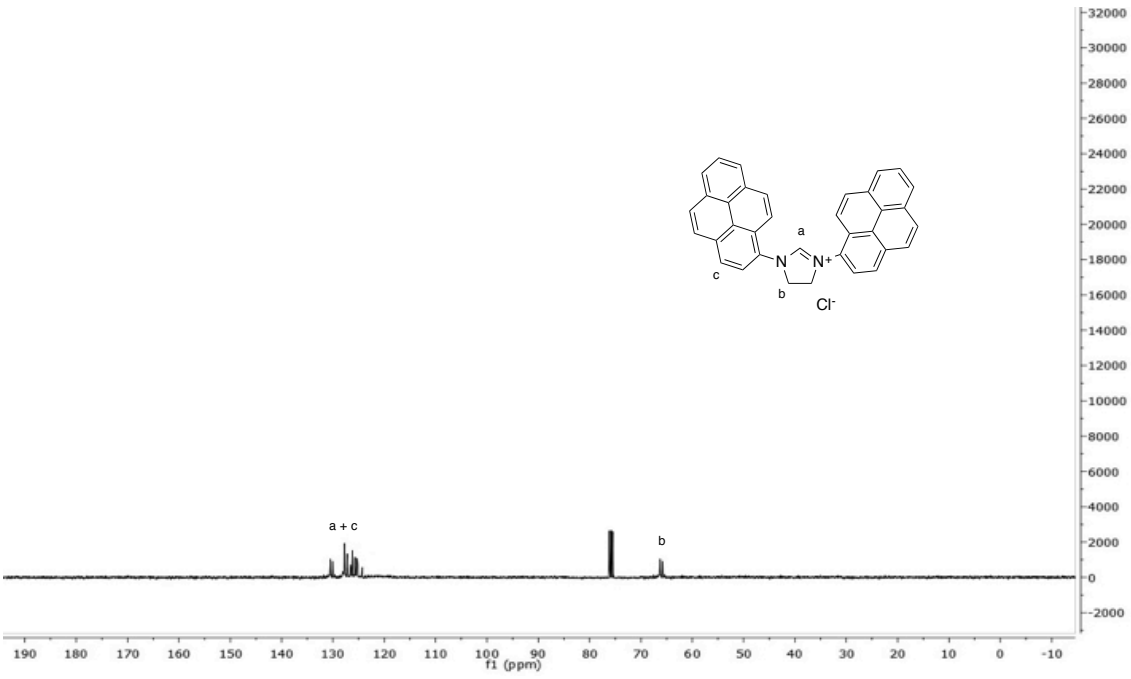




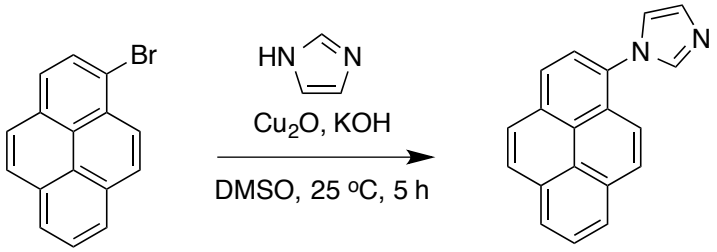
Preparation 1,3-Di(pyren-1-yl)-4,5-dihydro-imidazolium Chloride 32.

N,*N*'-Di(pyren-1-yl)ethane-1,2-diamine **31** (0.16 g, 0.3 mmol) was dissolved in 10 mL of trimethyl orthoformate. 4N HCl in dioxane (0.25 mL, 1 mmol) was added to solution then the mixture was refluxed using air condenser to remove methanol until completion (18 h). The precipitated solid was filtered and washed with ether (3 x 10 mL) to give dry product **32** (0.12 g, 0.23 mmol, 78%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.63 (1H, m), 8.55-8.50 (2H, m), 8.40 (1H, d, J = 6.3 Hz), 8.40-8.19 (11H, m), 8.12-8.06 (7H, m), 4.03 (4, t, J = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 129.5, 127.2 (2 peaks), 126.6 (2 peaks), 126.5 (2 peaks), 126.4, 126.3, 126.2, 125.7, 125.3, 125.1, 124.3, 123.1, 65.1, 64.7. MS (ESI): Exact mass calcd for $C_{35}H_{23}N_2Cl$ *ie* $[M+]^+$ 471.18 Found 471.18.


a + c
b
a
c
b
Cl-
f1 (ppm)


a + c
b
a
c
b
Cl-
f1 (ppm)

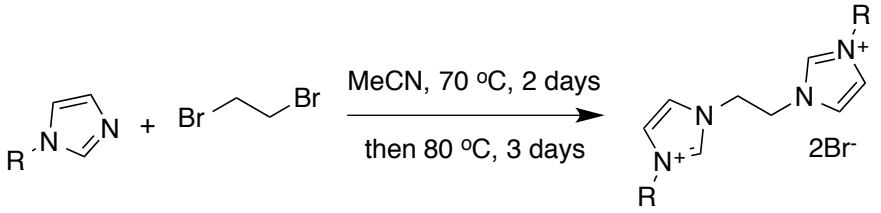
Preparation *N*-Pyrene imidazole 51.



51

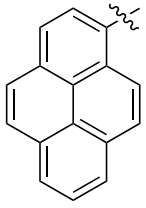
To a solution of 1-bromopyrene (0.56 g, 1 mmol) and imidazole (0.20 g, 3 mmol) in DMSO (10 mL), Cu_2O (0.03 g, 0.4 mmol) and KOH (0.23 g, 4 mmol) was added at 25 °C. The mixture was stirred for 5 h then passed through celite to remove remaining solid. Solvent was removed under reduced pressure then the residue was purified by chromatography using 20 % EtOAc/hexane as eluent to give compound **51** (0.14 g, 0.6 mmol, 55 %) as a yellow solid.

Preparation 1,2-Di(*N*-pyreneimidazole)ethane 52.



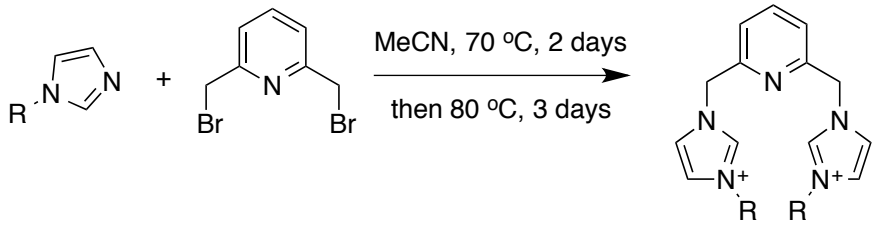
51 **52**

R =

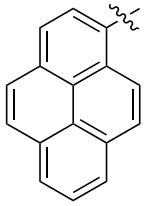


1-Pyrenyl-imidazole **51** (0.27 g, 1 mmol) and 1,2-dibromoethane (43 μL, 0.5 mmol) were dissolved in dry MeCN under Ar. The mixture was stirred at 70 ^oC for 2 days then heated to 80 ^oC for another 3 days. The mixture was allowed to ambient temperature then solvent was removed under reduced pressure. The residue was washed with Et_2O (3 x 5 mL). The product **52** was used without further purification.

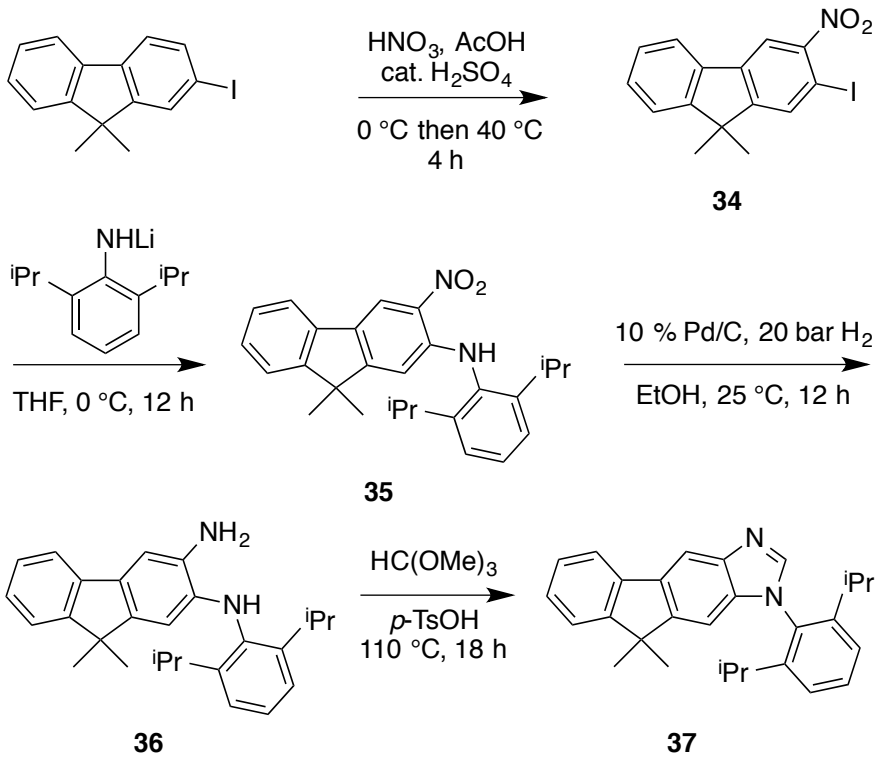
Preparation 1,1'-(Pyridine-2,6-diylbis(methylene))bis(3-pyrenyl-imidazolium) 53.



51 **53**

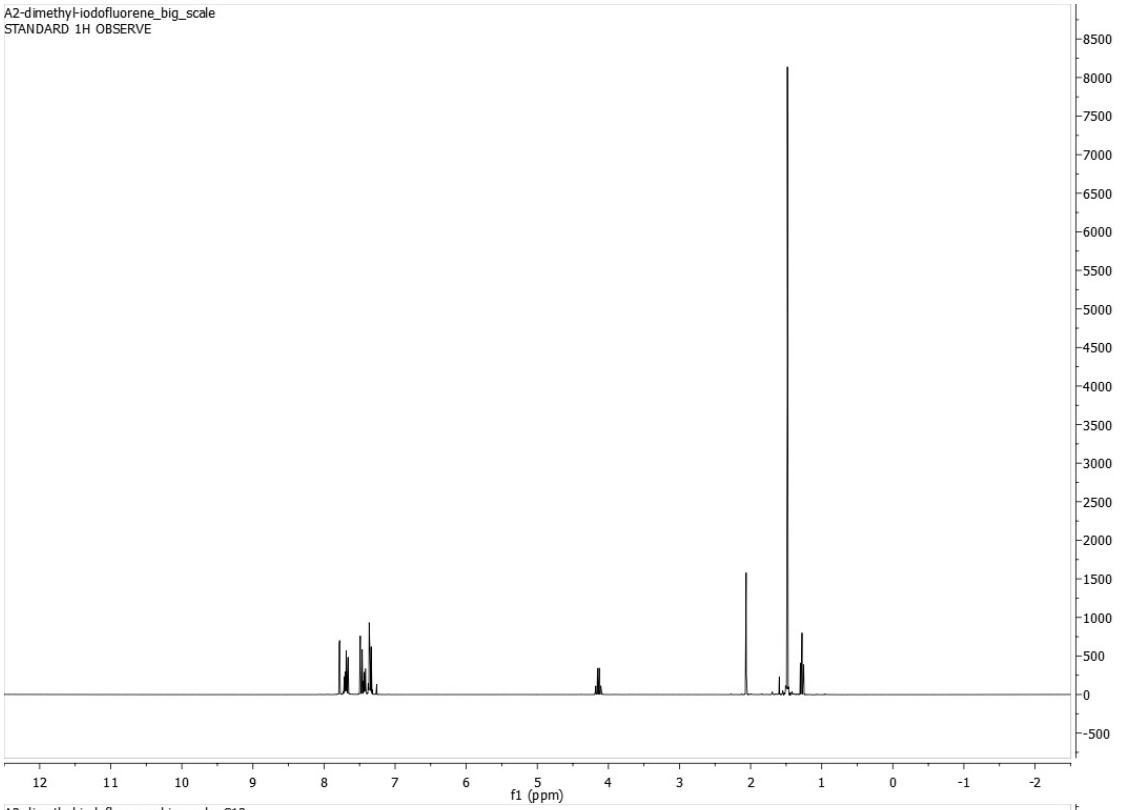
R = 

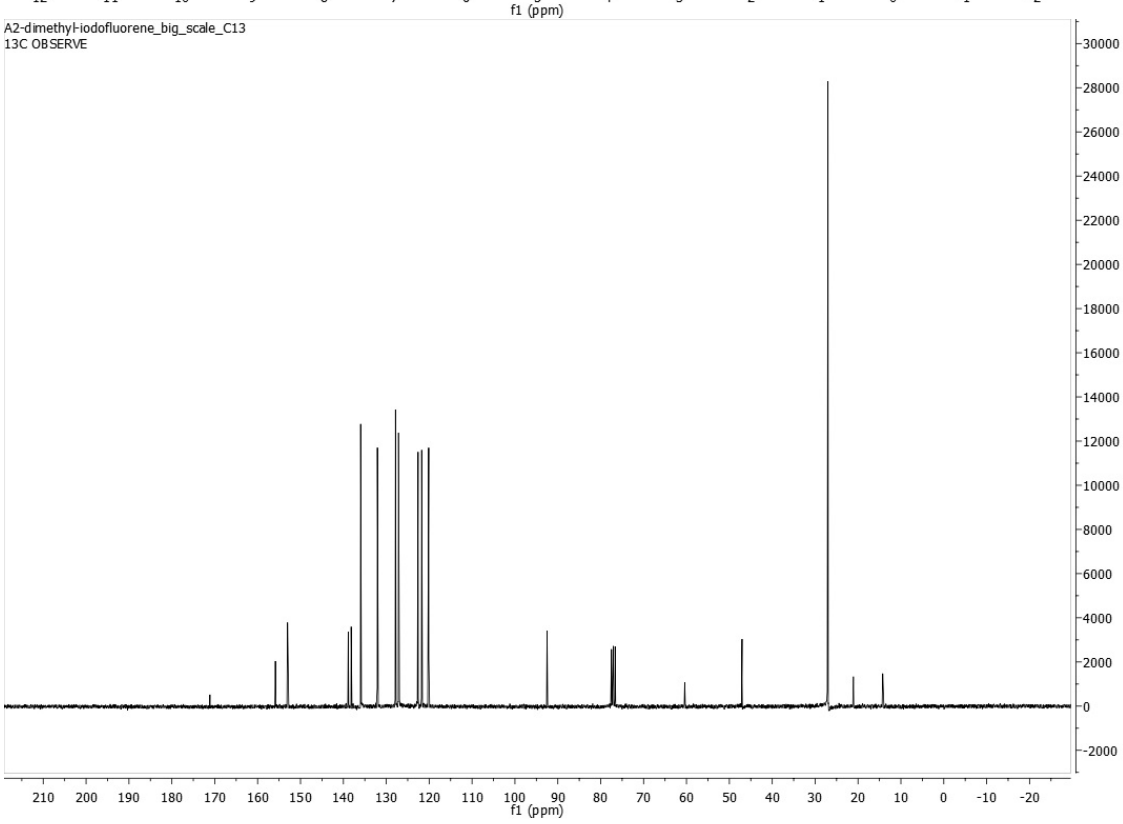
1-Pyrenyl-imidazole **51** (0.64 g, 2.4 mmol) and 2,6-bis(bromomethyl)pyridine (0.27 mg, 1 mmol) were dissolved in MeOH under Ar. The mixture was stirred at 70 ºC for 2 days then heated to 80 ºC for another 3 days. The mixture was allowed to cool to ambient temperature then solvent was removed under reduced pressure. The residue was washed with Et_2O (3 x 5 mL). The light yellow product **53** (0.7 g, 0.9 mmol, 40 %) was used without further purification.



Preparation 2-Iodo-9,9-dimethylfluorene.

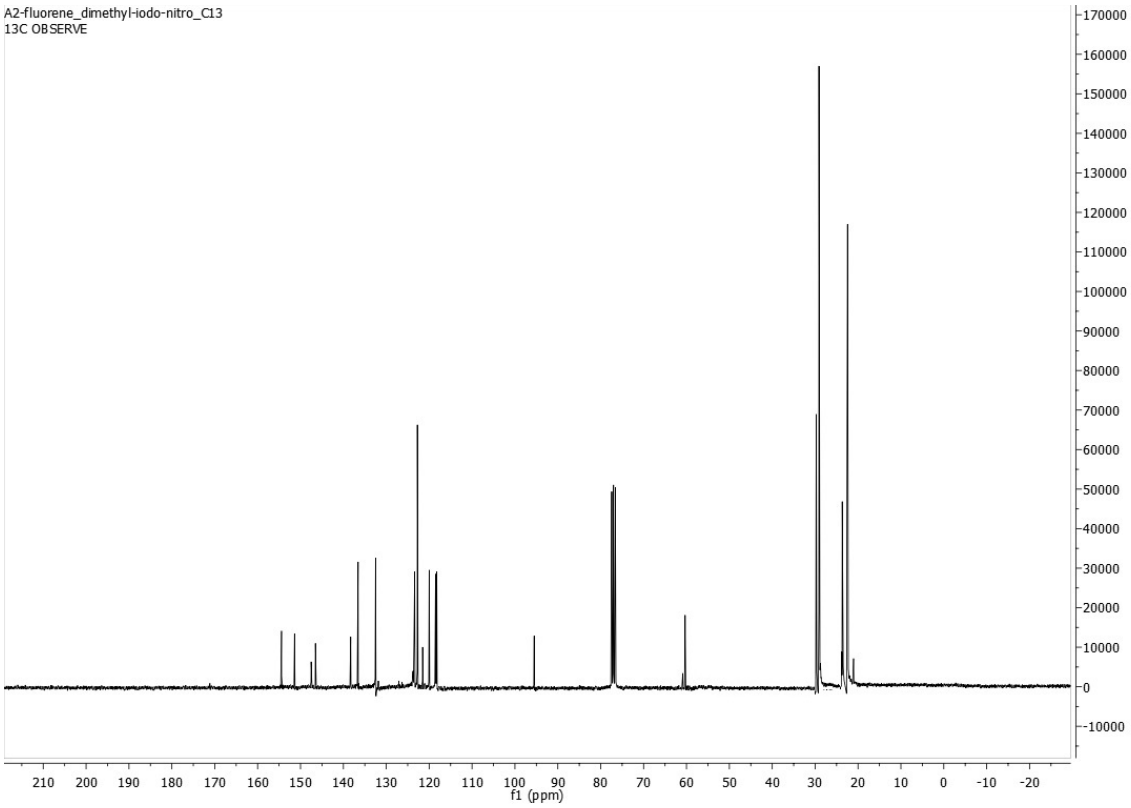
To a solution of 2-iodofluorene (0.95 g, 3.2 mmol) in 30 mL of THF, ^{t}BuOK (2.19 g, 19.5 mmol) was added at 0 ºC. The mixture was stirred for 30 min then warmed to ambient temperature. Alkylhalide (3 equiv) was added to the mixture. The reaction was stirred for another 6 h then water (30 mL) was added. The mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by chromatography using 10 % EtOAc/hexane as eluent to give product (92 %) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, d, J = 1.5 Hz), 7.75-7.69 (2H, m), 7.53-7.50 (1H, m), 7.48-7.45 (1H, m), 7.41-7.37 (2H, m), 1.52 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.0, 138.9, 138.2, 136.0, 132.1, 127.9, 127.2, 122.6, 121.8, 120.2, 92.6, 47.1, 27.0.

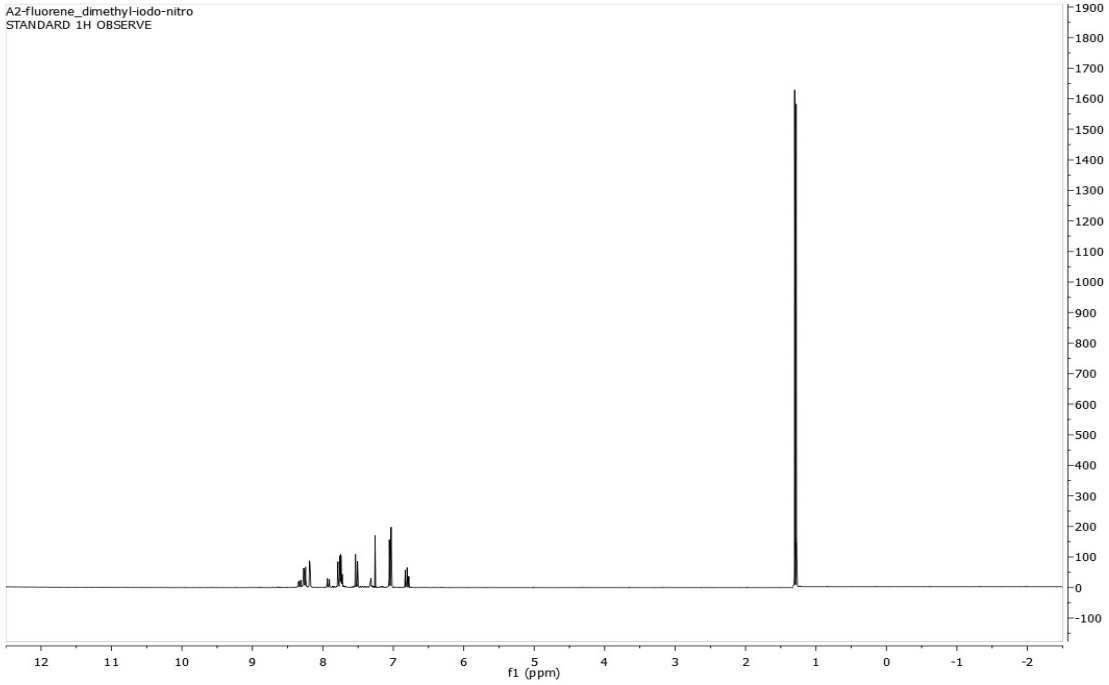

A2-dimethyl-iodofluorene_big_scale
STANDARD 1H OBSERVE
f1 (ppm)


A2-dimethyl-iodofluorene_big_scale_C13
13C OBSERVE
f1 (ppm)

Preparation 2-Iodo-9,9-dimethyl-3-nitrofluorene 34.

To a solution of 2-iodo-9,9-dimethylfluorene (0.95 g, 3.2 mmol) in 20 mL of AcOH, conc. HNO_3 was added at 0 ºC followed by catalytic amount of H_2SO_4. The mixture was stirred and heated to 40 ºC for 4 h. After allowed to cool to ambient temperature, the mixture was poured into saturated Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by chromatography using 30 % EtOAc/hexane as eluent to give product **34** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38-8.24 (1H, m), 8.18 (1H, d, *J* = 1.5 Hz), 7.76-7.72 (2H, m), 7.53 (1H, d, *J* = 8.4 Hz), 6.80 (1H, t, *J* = 7.8 Hz), 1.29 (3H, s), 1.27 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 151.4, 146.5, 138.3, 136.6, 132.5, 123.4, 122.7, 120.0, 118.5, 118.2, 95.5, 60.4, 29.1, 22.4. MS (ESI): Exact mass calcd for $C_{15}H_{12}INO_2$ *ie* $[M]^+$ 364.99. Found 364.99.

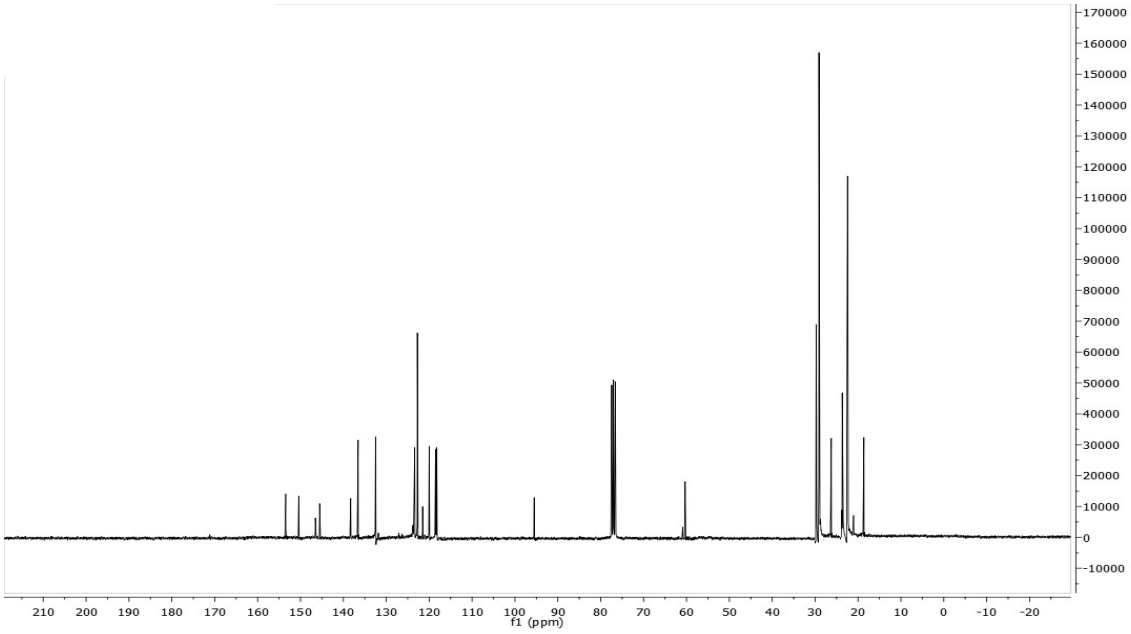


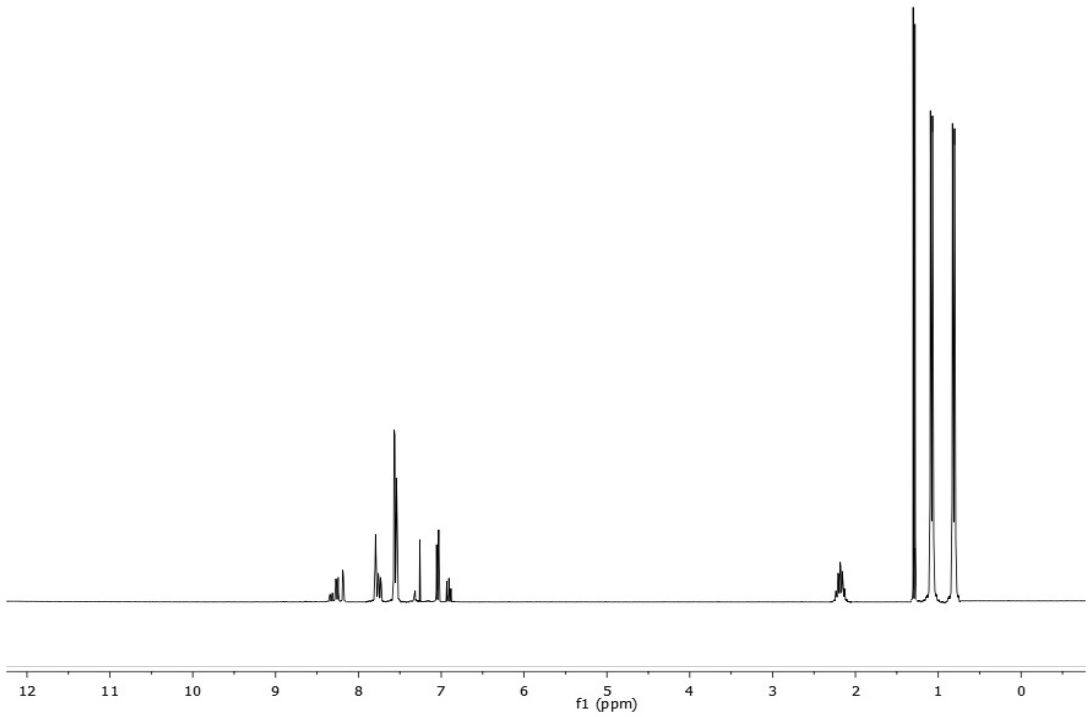


Preparation *N*-2,6-Diisopropylphenyl-9,9-dialkyl-3-nitrofluoren-2-amine 35

To a solution of 2,6-diisopropylaniline in THF, 2.5 M n-BuLi was added at 0 ºC. The reaction mixture was stirred for 30 min then transferred to a rapidly stirred solution of 2-iodo-9,9-dialkyl-3-nitrofluorene **34** in THF via cannula. The mixture was allowed to warm to ambient temperature and stirred for 12 h. Water was added dropwise to the mixture, then extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was purified by chromatography using 10 % EtOAc/hexane as eluent to give product **35** (65 %) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32-8.21 (2H, m), 8.15-6.82 (7H, m), 2.12 (2H, m), 1.27 (3H, s), 1.25 (3H, s), 1.12 (6H, d, J = 6.6 Hz), 0.98 (6H, d, J = 6.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 151.2, 150.3, 146.8, 146.5, 138.3, 136.6, 135.4, 133.1, 132.5, 128.7, 123.4, 122.7, 121.8, 120.0, 118.5, 118.2, 95.5, 60.4, 29.1, 25.1, 22.4, 19.3. MS (ESI): Exact mass calcd for $C_{27}H_{30}N_2O_2$ *ie* $[M+H]^+$ 415.24. Found

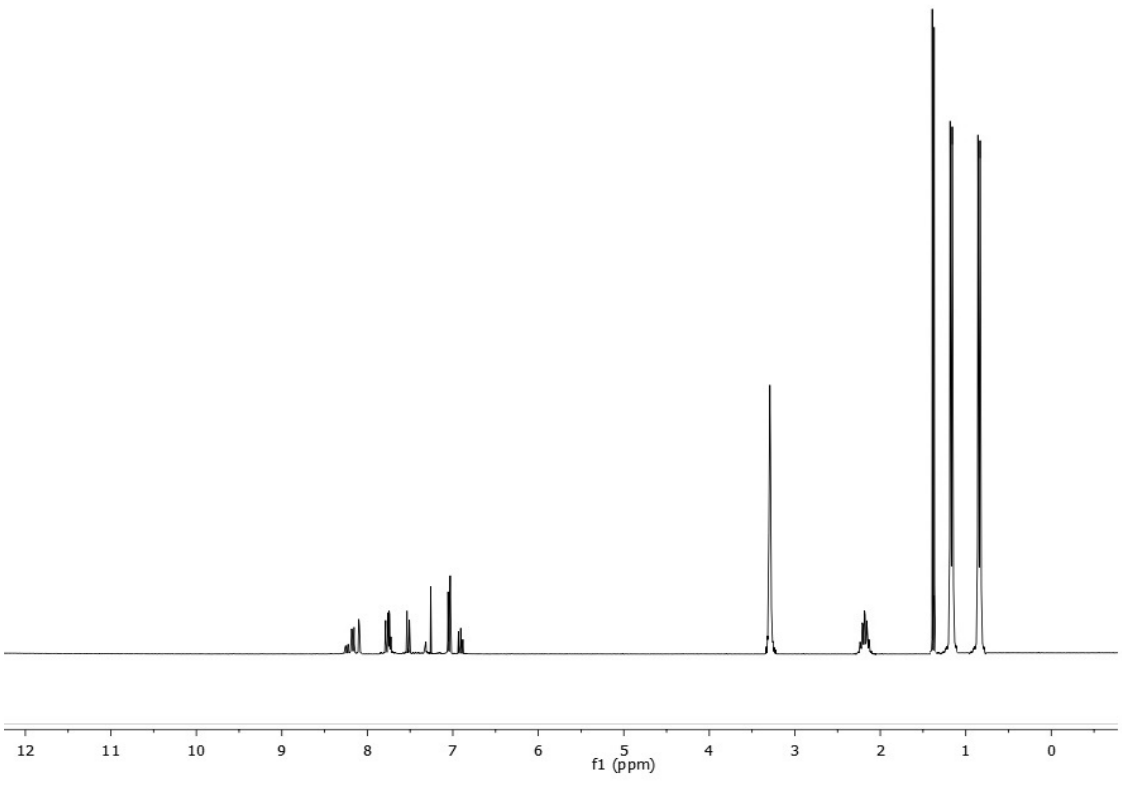
415.24.

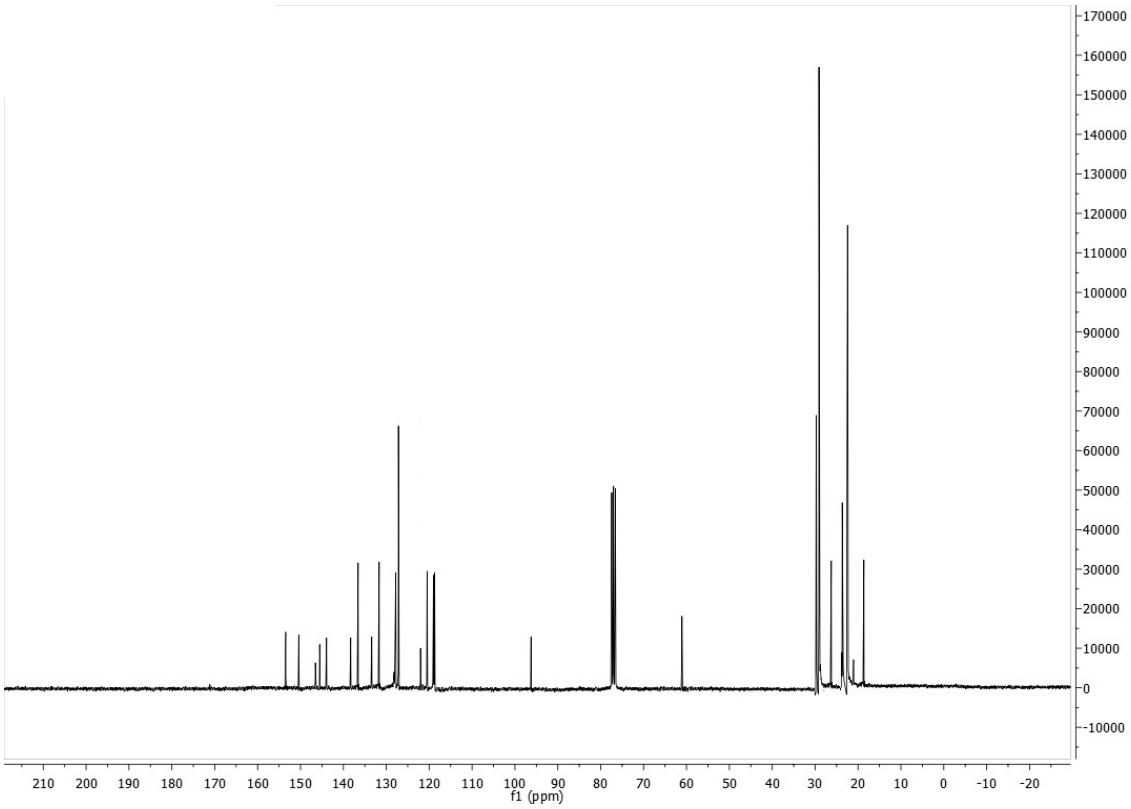

170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

Preparation of N^2-(2,6-Diisopropylphenyl)-9,9-dialkyl-fluorene-2,3-diamine 36.

10 % Pd/C (0.02 g, 0.02 mmol) was added to solution of *N*-2,6-diisopropylphenyl-9,9-dialkyl-3-nitrofluoren-2-amine **35** (0.65 g, 2 mmol) in 15 mL of EtOH. The mixture was then placed into pressure bomb and then flushed with H_2. The reaction was stirred under 20 bar of H_2 for 12 h. The mixture was passed through celite and the solvent was removed under reduced pressure to yield compound **36** (0.52 g, 1.96 mmol, 98%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38-8.25 (2H, m), 8.15-6.92 (7H, m), 2.21 (2H, m), 1.29 (3H, s), 1.24 (3H, s), 1.10 (6H, d, J = 6.6 Hz), 0.96 (6H, d, J = 6.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 151.2, 150.4, 146.8, 146.7, 138.3, 136.6, 135.4, 133.1, 132.5, 128.7, 123.4, 122.9, 122.8, 122.7, 121.8, 120.0, 118.5, 118.2, 95.5, 61.4, 29.5, 25.2, 22.8, 19.4. MS (ESI): Exact mass calcd for $C_{27}H_{32}N_2$ *ie* $[M+2H]^{2+}$ 193.14. Found 193.14.

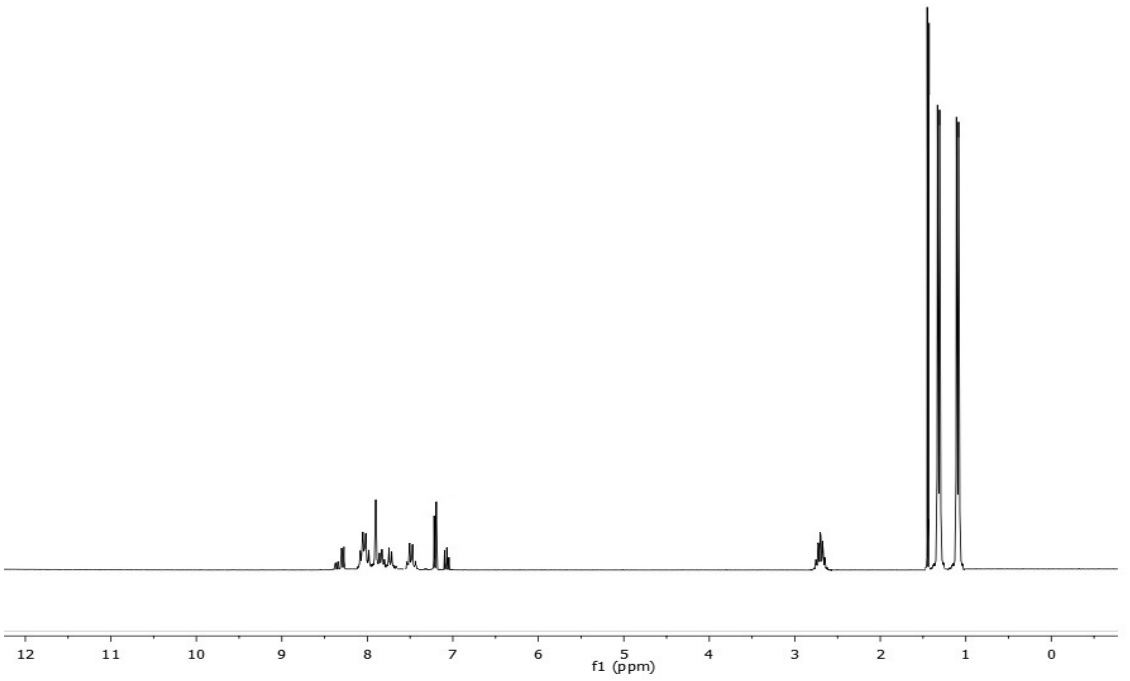


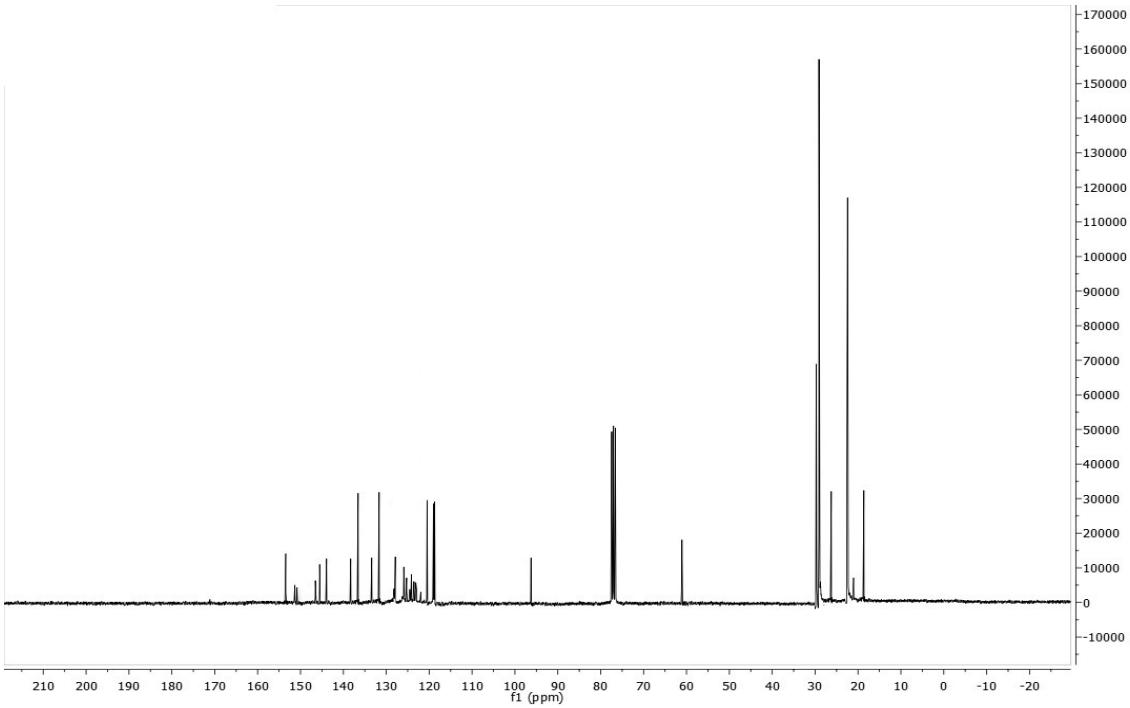


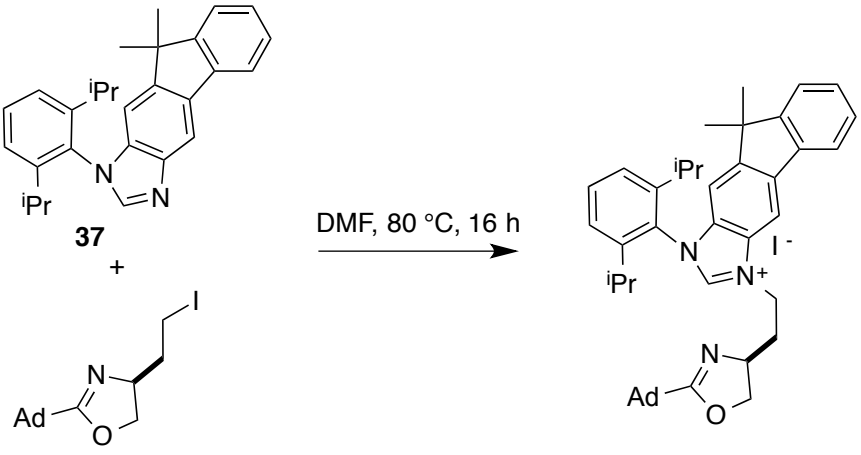
Preparation of 1-(2,6-diisopropylphenyl)-9,9-dimethyl-1,9-dihydrofluoreno[2,3-*d*]imidazole 37.

N^2-(2,6-Diisopropylphenyl)-9,9-dialkyl-fluorene-2,3-diamine **36** (0.60 g, 2.3 mmol) was dissolved in 5 mL of trimethyl orthoformate. Catalytic amount of *p*-toluenesulfonic acid (0.002 g, 0.01 mmol) was added to solution then the mixture was refluxed using air condenser to remove methanol until completion (18 h). Solvent was removed under reduce pressure and the residue was purified by chromatography using 20 % EtOAc/hexane as eluent to give **37** (0.19 g, 0.69 mmol, 30%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45-8.26 (2H, m), 8.18-7.05 (8H, m), 2.94-2.43 (2H, m), 1.44 (3H, s), 1.41 (3H, s), 1.32 (6H, d, J = 6.9 Hz), 1.23 (6H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 154.3, 151.2, 150.3, 146.8, 146.7, 138.5, 136.7, 135.4, 133.0, 132.5, 128.6, 123.4, 122.9, 122.8, 122.7, 121.6, 120.0, 119.3, 118.5, 96.3, 61.5, 30.2,

25.5, 22.5, 19.8. MS (ESI): Exact mass calcd for $C_{28}H_{30}N_2$ *ie* $[M+H]^+$ 395.25. Found 395.25.



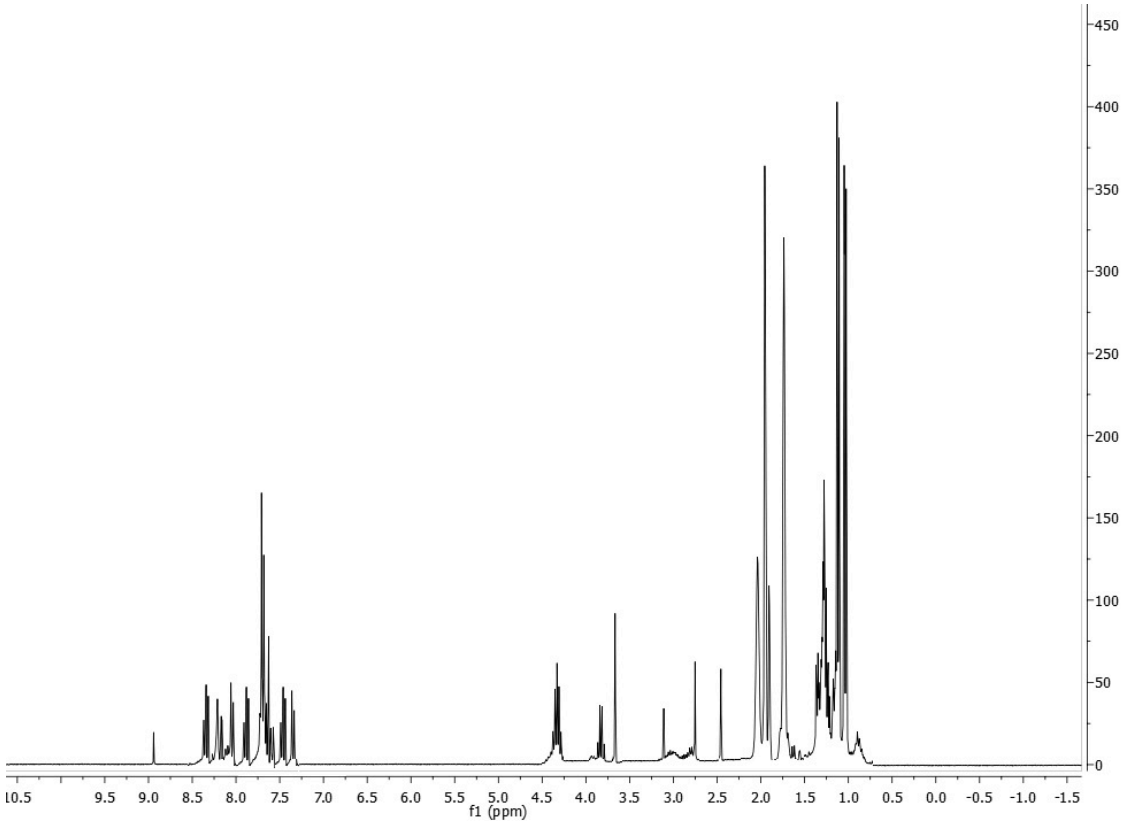


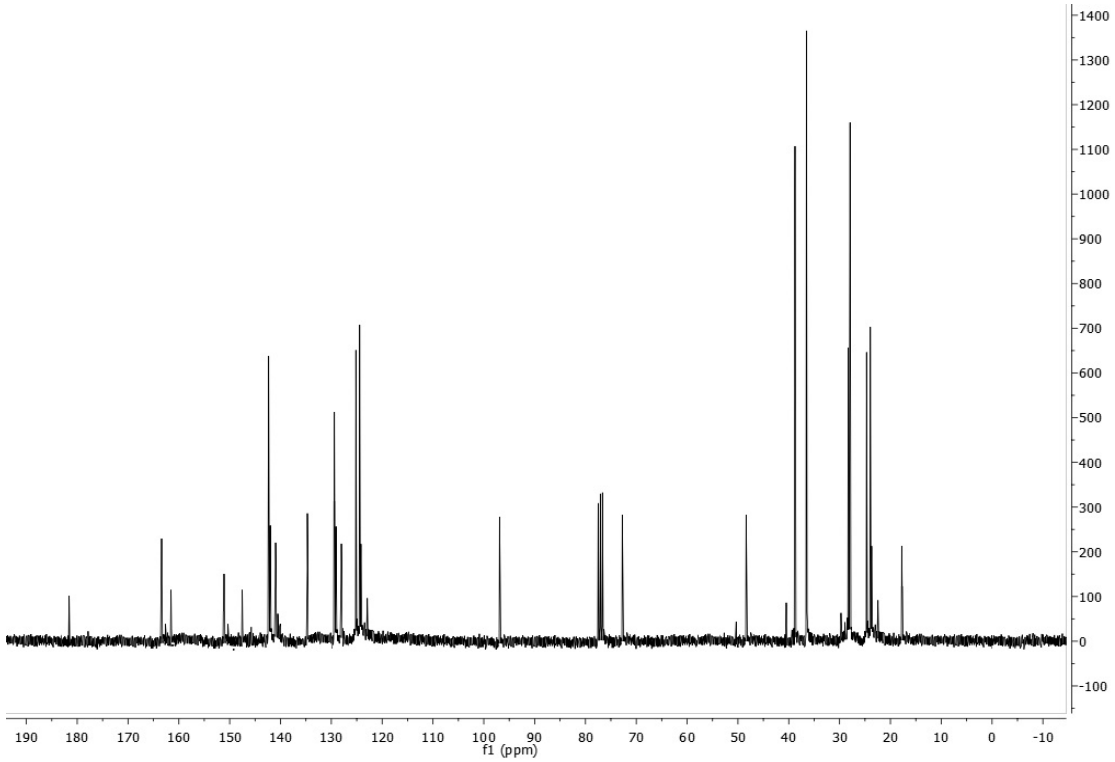


38

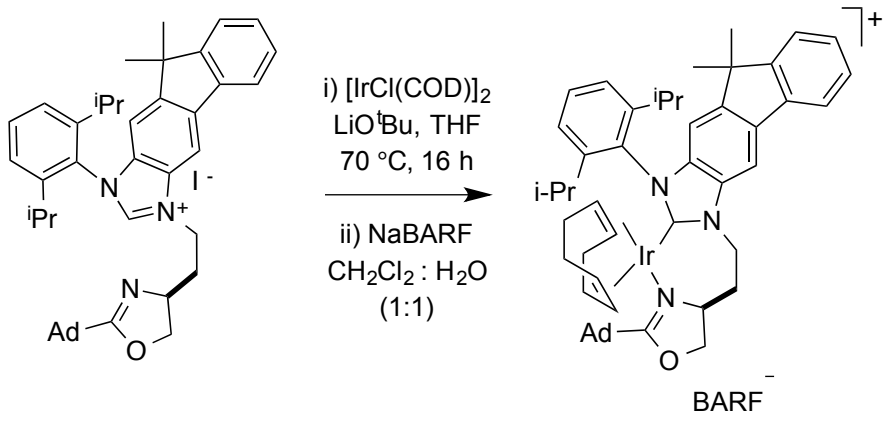
Preparation of Adamanyl Oxazoline imidazolefluorene iodide 38.

Adamantyl oxazoline iodide (1.80 g, 5 mmol) and 1-(2,6-diisopropylphenyl)-9,9-dimethyl-1,9-dihydrofluoreno[2,3-*d*]imidazole **37** (1.39 g, 5 mmol) was dissolved in 10 mL of DMF under Ar atmosphere. The mixture was heated to 80 ºC for 12 h. The solvent was removed under reduced pressure and the residue was washed with Et_2O (5 x 5 mL) to yield compound **38** (2.39 g, 3.8 mmol, 75%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.9 (1H, s), 8.42-8.25 (2H, m), 8.20-6.98 (7H, m), 4.43-4.10 (5H, m), 3.75 (2H, m), 3.05-2.95 (1H, m), 2.92-2.70 (3H, m), 2.47 (1H, s), 1.98-1.54 (15H, m), 1.25-1.09 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 164.8, 162.8, 161.9, 161.8, 151.2, 150.3, 147.0, 146.9, 142.7, 142.3, 141.5, 135.0, 129.6, 124.4, 123.4, 122.5, 95.1, 73.4, 50.7, 47.2, 38.9, 38.6, 37.3, 36.4, 28.2, 28.0, 27.4, 25.1, 24.1, 23.5, 22.3 18.7. MS (ESI): Exact mass calcd for $C_{43}H_{52}N_3O$+ *ie* $[M+]^+$ 626.41. Found 626.41.


450
400
350
300
250
200
150
100
50
0
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
f1 (ppm)

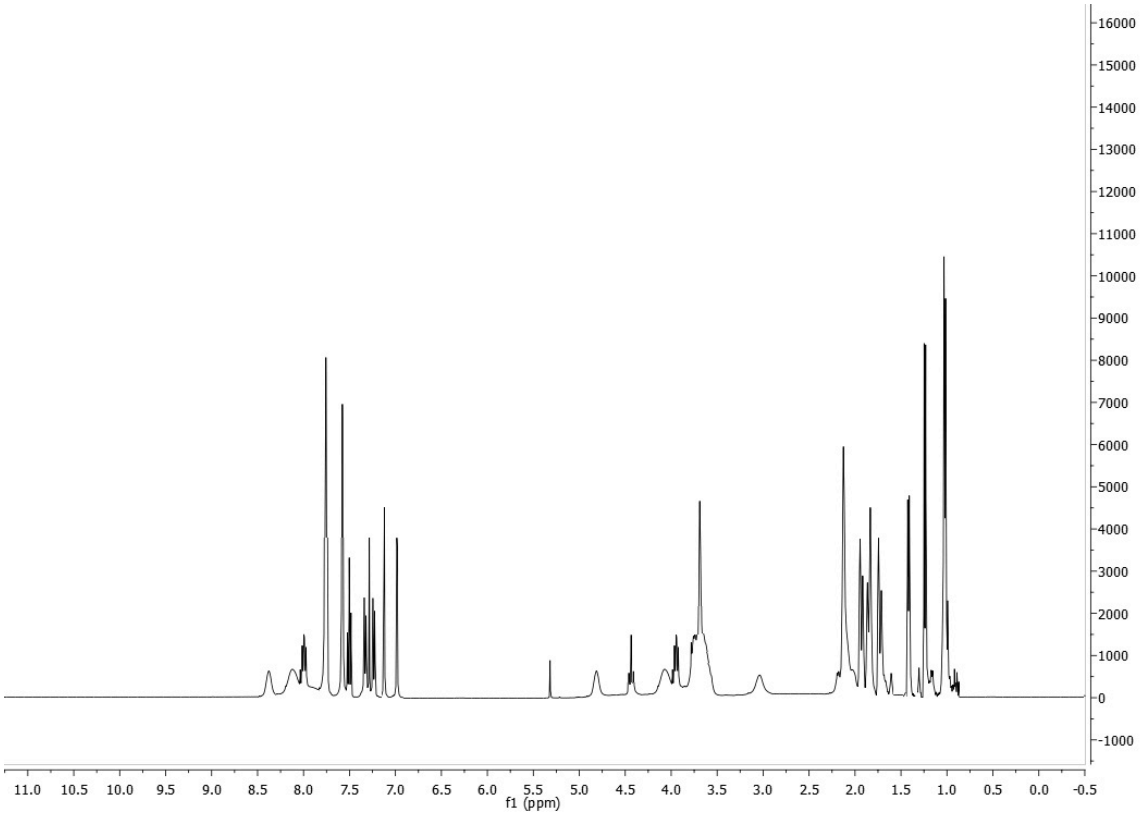

1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

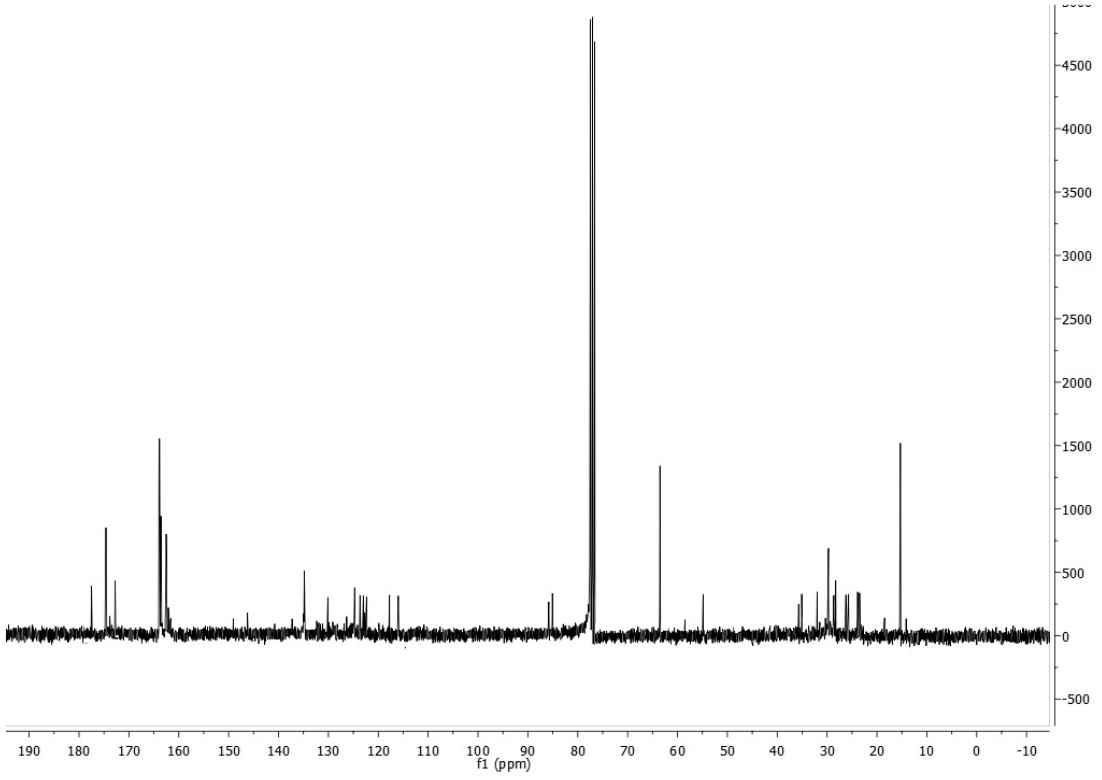
Preparation of Ir Complex 39.



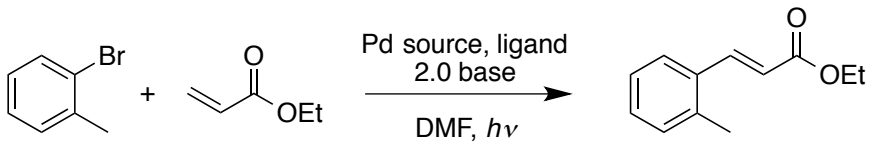
38 **39**

Imidazolinium salt **38** was added to a round bottom flask along with 1.5 equivalents lithium *tert*-butoxide and 0.5 equivalents of $[Ir(COD)Cl]_2$ under Ar. THF was syringed in to make the solution 0.03 M in imidazolinium salt. The mixture was heated to 70 ^{o}C in an oil bath and stirred for 16 h. After cooling to room temperature, the volatiles were removed under reduced pressure and 1.5 equivalents of NaBARF in 5 mL CH_2Cl_2 was added. Water (5 mL) was added and the mixture was stirred vigorously for 15 min. The organic layer was removed and the aqueous layer was washed with an additional 5 mL CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4) and the volatiles were removed in vacuo. The residue was chromatographed using a short silica column and 10 % hexanes/CH_2Cl_2 as the eluent to give **39** as a solid (32 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42-8.11 (2H, m), 8.20-7.90 (2H, m), 7.74 (8H, s), 7.57 (4H, 2), 7.41-7.30 (3H, m), 7.28-6.87 (2H, m), 4.73-4.68 (1H, m), 4.35-4.25 (2H, m), 4.16-4.12 (1H, m), 3.97-3.58 (6H, m), 3.46-3.38 (1H, m), 3.25-3.21 (1H, m), 2.95-2.89 (2H, m), 2.68-2.59 (1H, m), 2.17-1.59 (22H, m), 1.45-1.15 (17H, m), 0.95-0.84 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 177.5, 174.5, 163.6, 162.7, 162.0, 161.3, 160.7, 146.7, 136.3, 134,9, 134.8, 130.0, 129.2, 129.1, 128.7 (2 peaks), 128.6, 126.4, 124.8, 122.7, 117.5, 85.5, 62.1, 55.7, 30.2, 29.9, 29.1, 28.7, 27.4, 26.9, 25.4, 23.9, 22.9.


16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

B. General Procedure for Heck Coupling.



Pd source, base and ligand were dissolved in DMF under Ar in photoreactor. Acrylate and bromotoluene were added to solution then reaction mixture was stirred in the presence of light for 12 h. The mixture was passed through celite and solvent was removed under reduced pressure. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

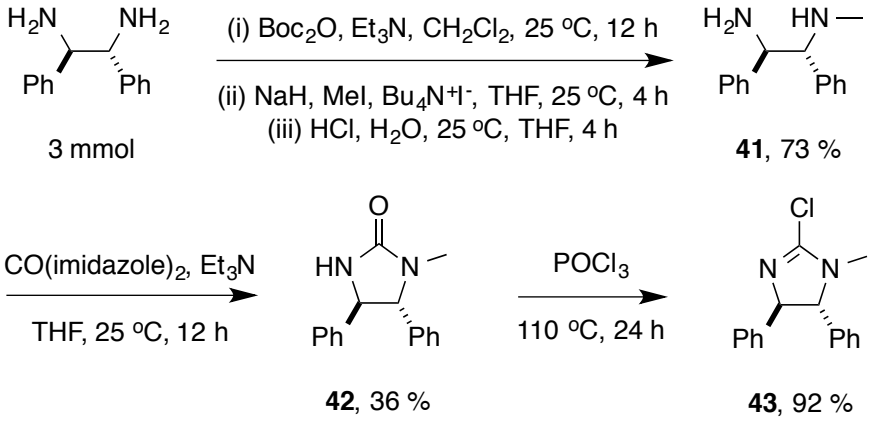
C. Catalytic Hydrogenation Conditions

The corresponding alkenes (0.25 mmol) and Ir-catalyst (1-2 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 10 - 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

APPENDIX G
EXPERIMENTAL FOR CHAPTER VII

A. Preparation of Catalysts 40.

Preparation of (4*R*,5*R*)-2-Chloro-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole 43.



(*S*,*S*)-*N*,*N'*-diBoc-1,2-diphenyl ethylenediamine

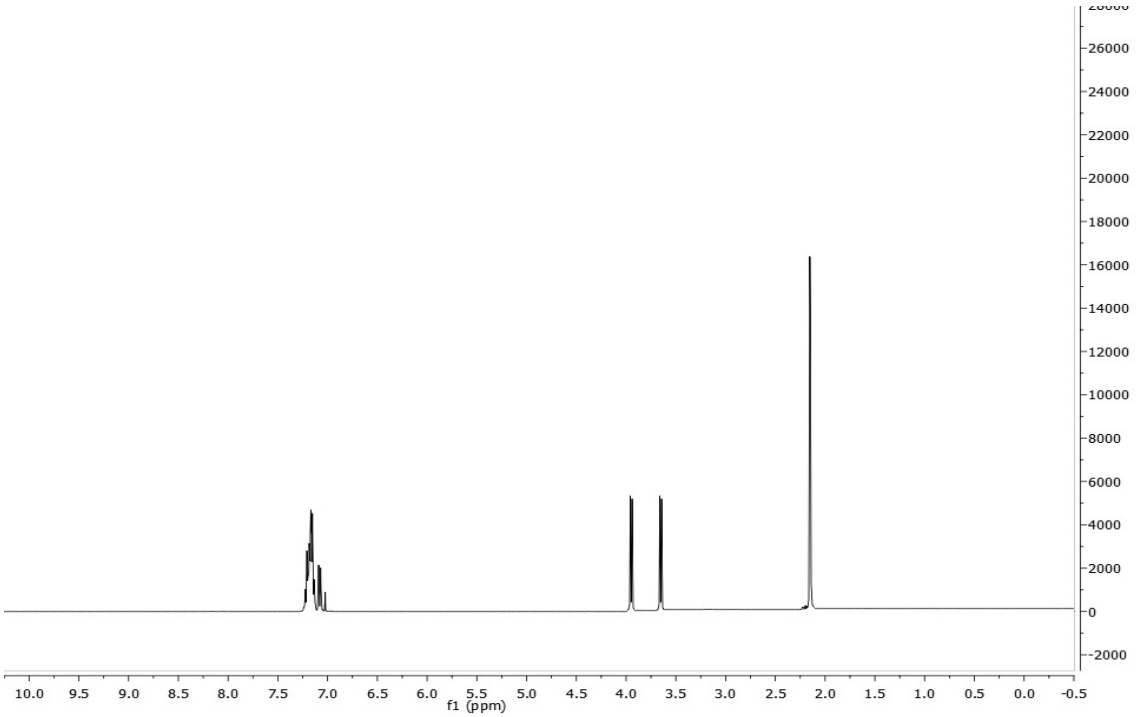
To a solution of (*S*,*S*)-1,2-diphenyl ethylenediamine (658 mg, 3.1 mmol) and triethyl-amine (3 mL, 22 mmol) in CH_2Cl_2 (20 mL) was added Boc_2O (1.6 mL, 7.0 mmol) at ambient temperature under Ar and stirred for 15 h. The resulting solution was diluted with CH_2Cl_2, poured into saturated NH_4Cl (aq), and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and evaporated in *vacuo*. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt = 10/1) to give product (1.228 g, 96 %) as colorless solid. mp: 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.14 (6H, m), 7.07-7.02 (4H, m), 5.58 (2H, br), 4.85 (2H, br), 1.44 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 139.2, 128.3, 127.5, 127.3, 79.7, 60.7, 28.3. HRMS (FAB): Exact mass calcd for $C_{24}H_{33}N_2O_4$ *ie* $[M+H]^+$ 413.2440. Found 413.2442.

(*S*,*S*)-*N*-methyl-1,2-diphenyl ethylenediamine 41.

To a solution of (*S*,*S*)-*N*,*N'*-diBoc-1,2-diphenyl ethylenediamine (1.027 g, 2.49 mmol), MeI (7.75 mL, 124 mmol), and TBAI (4.6 g, 12.5 mmol) in THF (20 mL) was

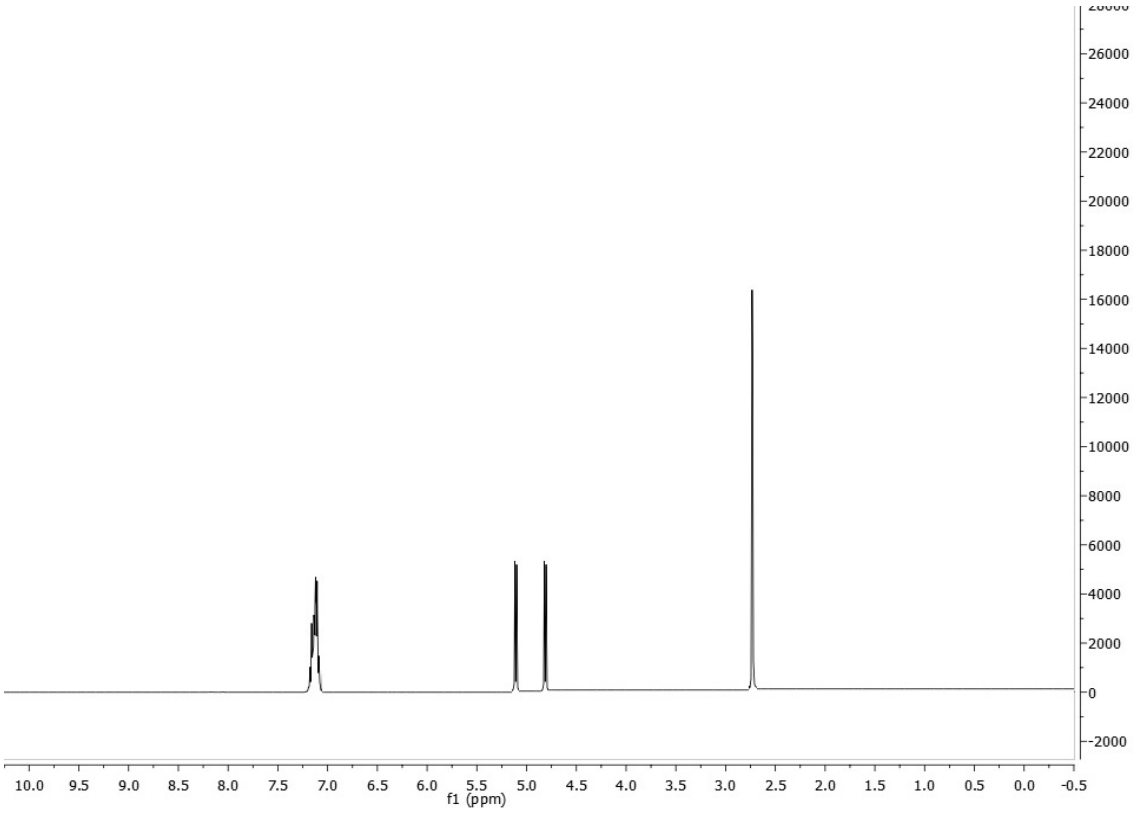
added NaH (110 mg, 60% in oil, 2.75 mmol) at 0 °C under Ar and stirred for 13 h at room temperature. The resulting solution was diluted with AcOEt, poured into saturated NH_4Cl (aq), and washed with H_2O and brine. Organic layer was dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hex/AcOEt = 5/1) to give (*S*,*S*)-*N*-methyl-*N*,*N'*-diBoc-1,2-diphenyl ethylenediamine (157 mg, 15 %) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.12 (10H, m), 5.77 (3H, br), 5.42 (7H, br), 2.66 (3H, s), 1.51 (9H, s), 1.41 (9H, s). HRMS (FAB): Exact mass calcd for $C_{25}H_{35}N_2O_4$ *ie* $[M+H]^+$ 427.2597. Found 427.2606.

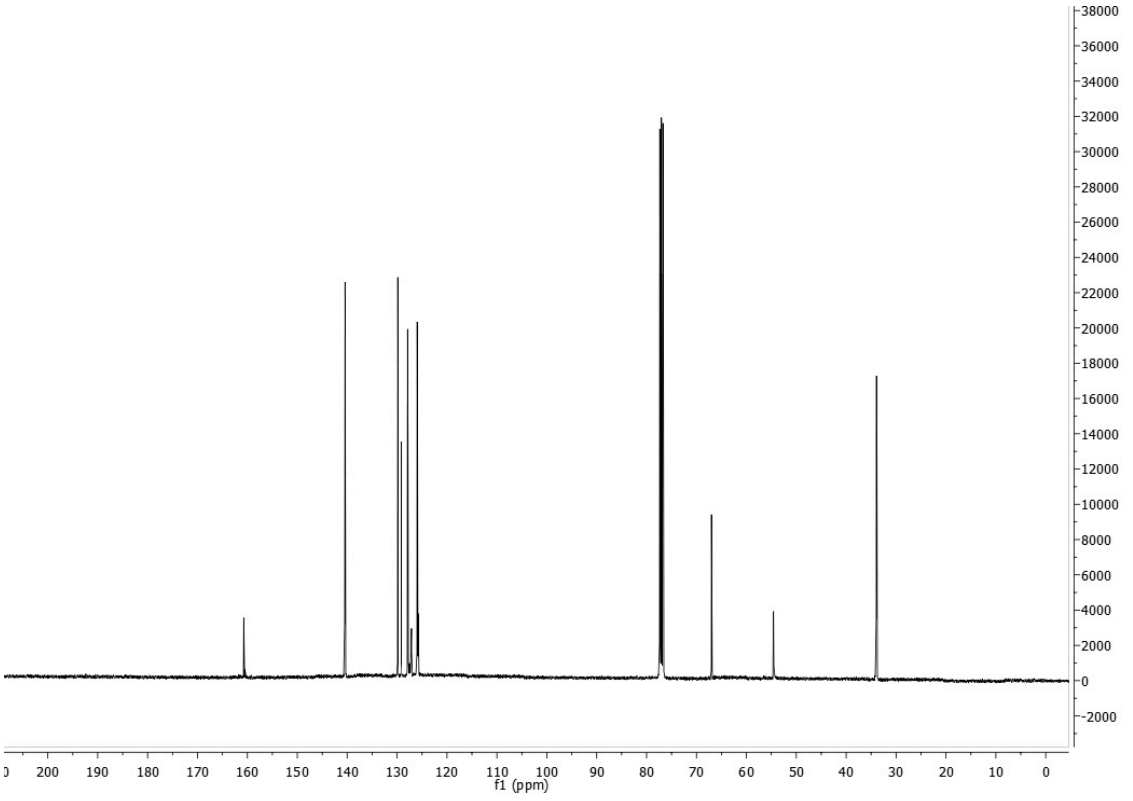
To a solution of (*S*,*S*)-*N*-methyl-*N*,*N'*-diBoc-1,2-diphenyl ethylenediamine (151.8 mg, 0.356 mmol) in THF (5 mL) was added 2N HCl aq. (5 mL) at room temperature and stirred for 1 h. The reaction mixture was added cHCl (2 mL) and stirred for 2 h. The resulting solution was diluted with Et_2O and extracted with 5 % H_2SO_4 (aq). Aqueous layer was basified with NaOH and extracted with CH_2Cl_2. Organic layer was dried over Na_2SO_4, and evaporated in vacuo to give **41** (75.1 mg, 93%) as colorless amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.11 (10H, m), 3.98 (1H, d, J = 6.9 Hz), 3.62 (1H, d, J = 6.9 Hz), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.9, 128.0, 127.90, 127.88, 126.93, 126.90, 126.8, 71.7, 61.6, 34.6. HRMS (FAB): Exact mass calcd for $C_{15}H_{19}N_2$ *ie* $[M+H]^+$ 227.1548. Found 227.1550.



(4*R*,5*R*)-1-methyl-4,5-diphenylimidazolidin-2-one 42.

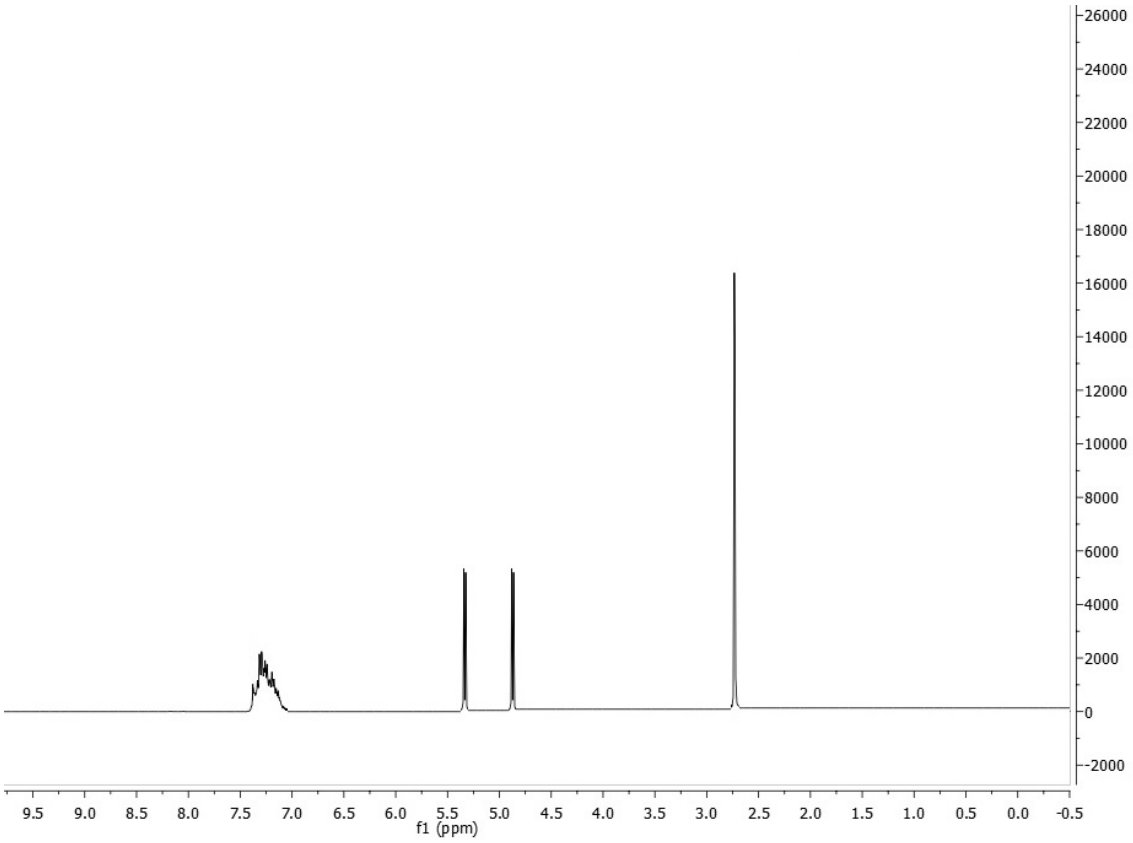
To a solution of (*S,S*)-*N*-methyl-1,2-diphenyl ethylenediamine **41** in THF, Et_3N was added. The solution was cooled to 0 °C, then 1,1-carbonyldiimidazole was added. The mixture was warmed to room temperature and stirred for another 12 h. Water was added and aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers was washed with 1N HCl, saturated $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was purified by chromatography (EtOAc/hexane and EtOAc/ether) to give (4*R*,5*R*)-1-methyl-4,5-diphenylimidazolidin-2-one **42** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.10 (10H, m), 5.12 (1H, d, *J* = 6.9 Hz), 4.78 (1H, d, *J* = 6.9 Hz), 2.75 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 140.5, 128.4, 127.9, 127.0, 126.9, 126.8, 126.5, 65.3, 54.1, 34.7.

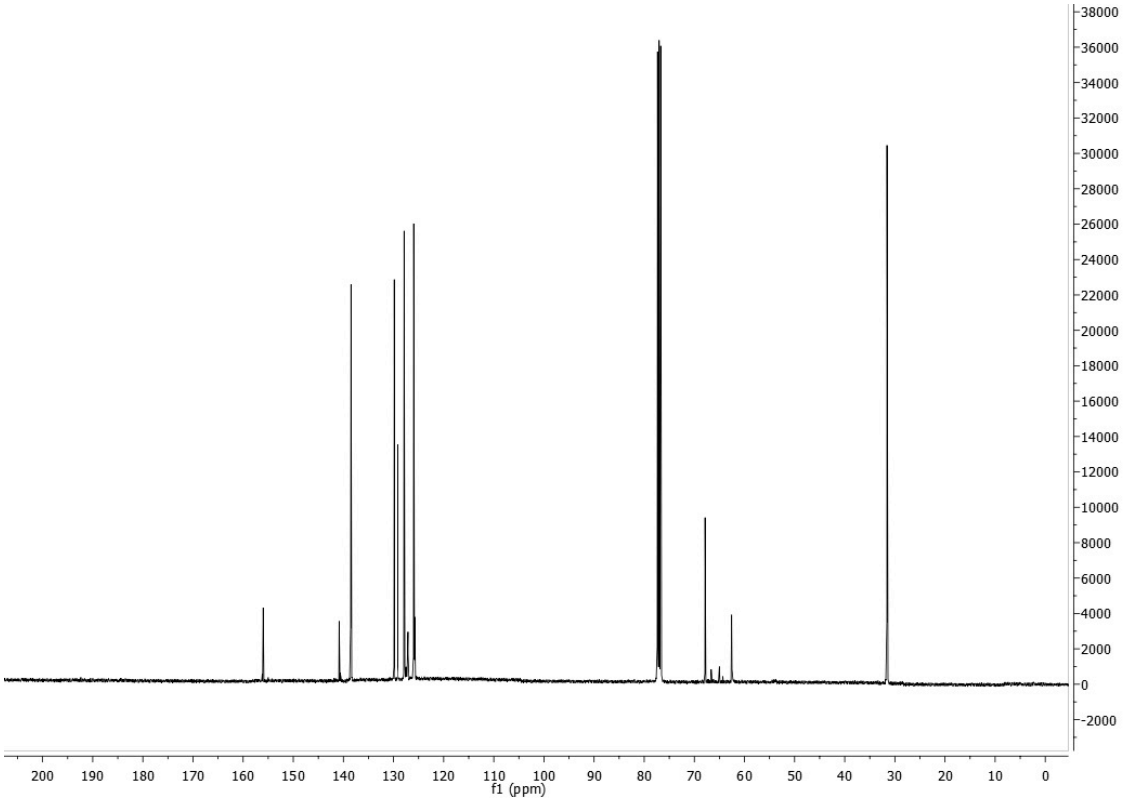

26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

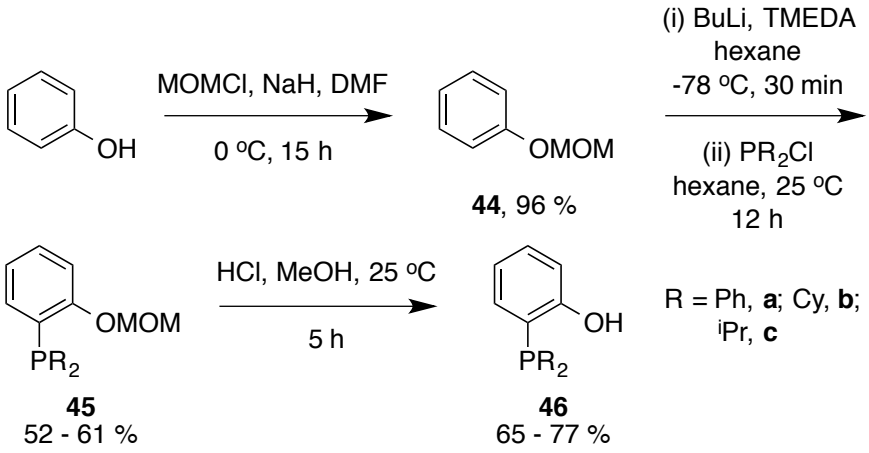
(4*R*,5*R*)-2-chloro-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole 43.

(4*R*,5*R*)-1-methyl-4,5-diphenylimidazolidin-2-one **42** was dissolved in $POCl_3$. The solution was refluxed for 24 h and then cooled to ambient temperature. The mixture was poured into iced-cool 1N NaOH (aq) and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by chromatography using EtOAc/hexane to give product as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (10H, m), 5.27 (1H, d, J = 6.9 Hz), 4.89 (1H, d, J = 6.9 Hz), 2.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 140.2, 138.5, 128.6, 128.0, 127.9, 127.5, 126.9, 126.7, 126.8, 125.9, 68.3, 63.1, 30.7.





General Procedure for Preparation of 2-(Dialkylphosphino)phenol 46.



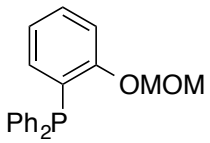
Synthesis of methoxymethyl phenyl ether 44.

At 0 °C and with stirring, phenol (5 g, 53.1 mmol, 1 eq) was added to NaH (1.91 g, 79.7 mmol, 1.5 eq) in dimethylformamide (26.5 mL, 2 M). After 30 min,

chloromethyl methyl ether (6.05 mL, 79.7 mmol, 1.5 eq) was added, then the temperature was allowed to warm up to room temperature. The mixture was stirred and the reaction was monitored by TLC (8:2 hexane/AcOEt). After 30 minutes, water (106 mL) was added. The product was exctracted with hexane (3 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The product was purified by distillation (p = 1.5 Torr, T = 30 – 32 °C) to give colorless oil (74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (11H, m), 7.13 (1H, m), 6.93 (1H, m), 6.72 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 136.9, 134.4, 134.0, 133.7, 130.4, 128.9, 128.7, 128.5, 122.2, 113.6, 113.6, 94.3, 56.1.

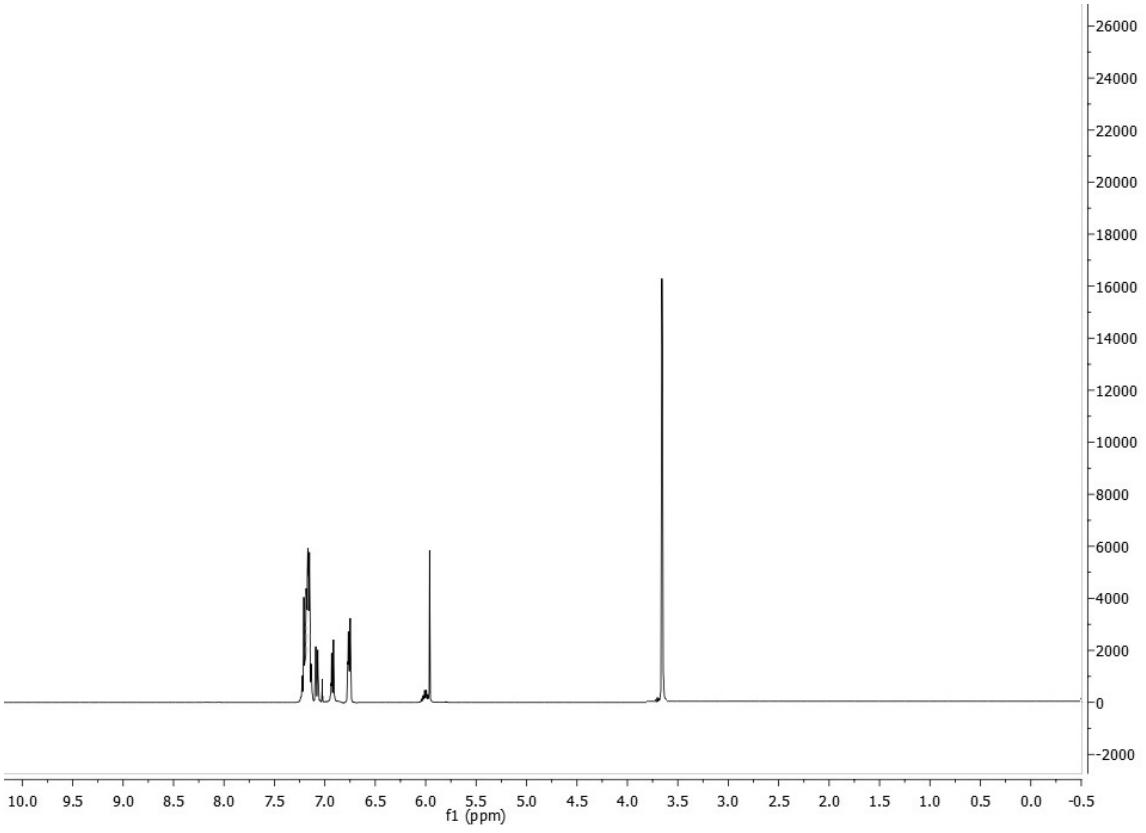
General Procedure for Synthesis of Methoxymethyl *o*-dialkylphosphinophenyl ether 45.

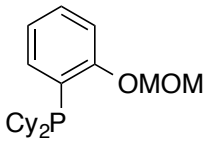
A solution containing 1.6 M *n*-BuLi (10 mL, 16 mmol, 1.1 eq) and *N,N,N',N'*-tetra-methylethylenediamine (2.24 mL, 14.9 mmol, 1.03 eq) in dry hexane was added to an ice-cooled solution of methoxymethyl phenyl ether (2 g, 14.5 mmol, 1 eq) in dry hexane under Ar. The mixture was allowed to warm up to room temperature. The solution became yellow and a pale precipitate formed after 1.5 h. The solution was cooled in ice and appropriate chlorodialkylphosphine (1 eq) was added slowly. The resultant solution was stirred for 16 h at room temperature and the solvent was removed under reduced pressure. The residue was diluted with Et_2O and washed with 1 M aqueous Na_2HPO_4. The organic layer was dried over Na_2SO_4 and concentrated to give a white solid. The solid was dissolved in MeOH. After cooling for 30 minutes, the crystals were collected and recrystallized from CH_2Cl_2/MeOH.



45a

Methoxymethyl *o*-diphenylphosphinophenyl ether 45a. 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (11H, m), 7.13 (1H, m), 6.93 (1H, m), 6.72 (1H, m), 5.98 (2H, s), 3.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 136.9, 134.4, 134.0, 133.7, 130.4, 128.9, 128.7, 128.5, 122.2, 113.6, 113.6, 94.3, 56.1; ^{31}P-NMR (161 MHz, $CDCl_3$) δ -14.8.

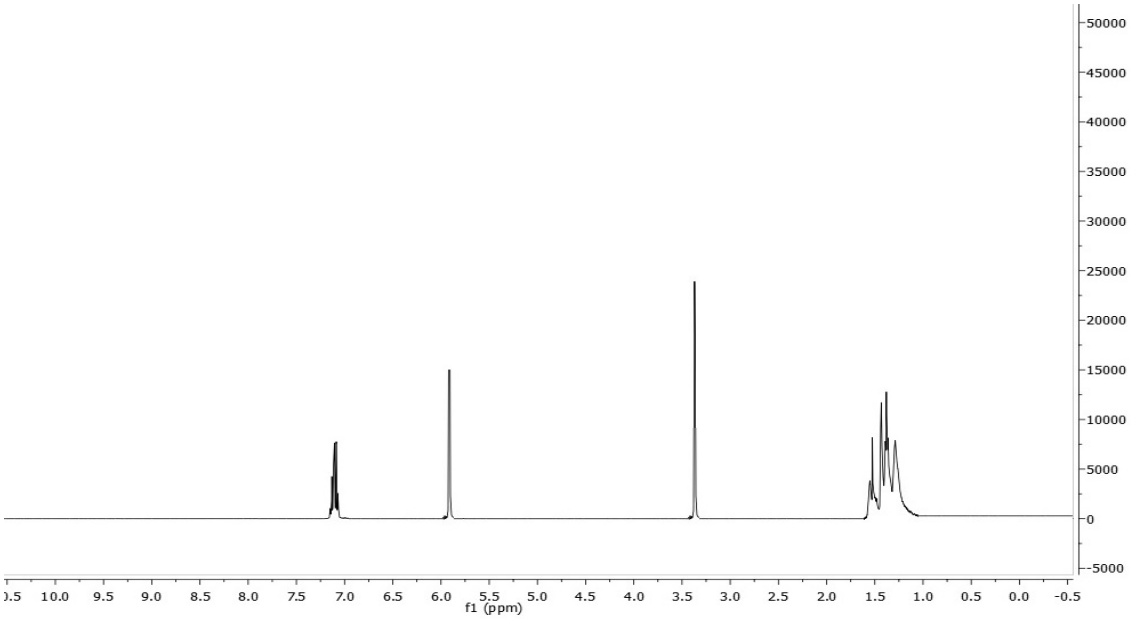


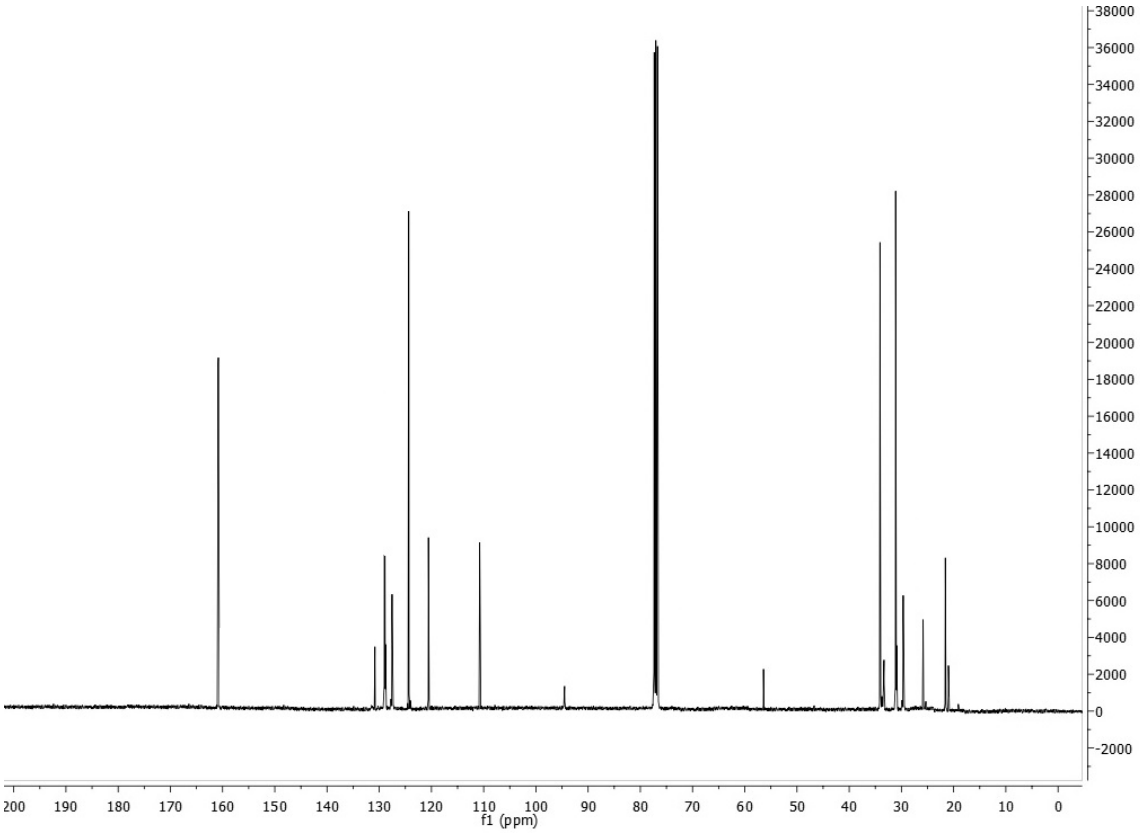


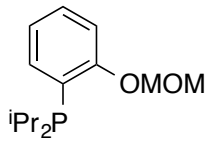
45b

Methoxymethyl *o*-dicyclohexylphosphinophenyl ether 45b. 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.10 (4H, m), 5.97 (2H, s), 3.41 (3H, s), 1.58-1.10 (22H, m); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 160.1, 130.1, 129.8, 129.7, 128.7, 124.1, 121.1, 110.5, 95.2, 55.5, 34.3, 30.1, 29.0, 28.9, 26.0.

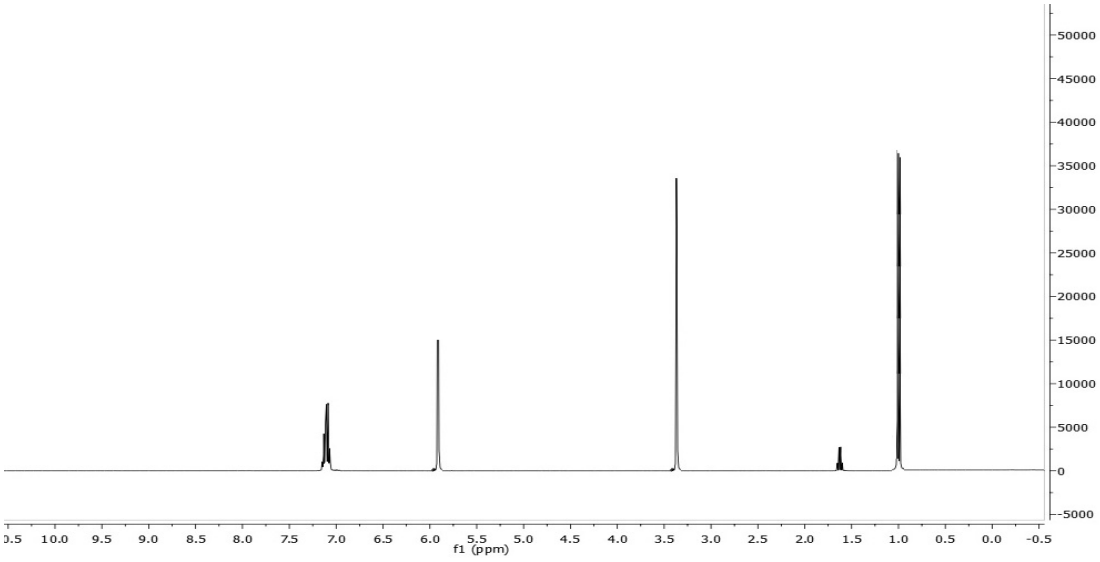


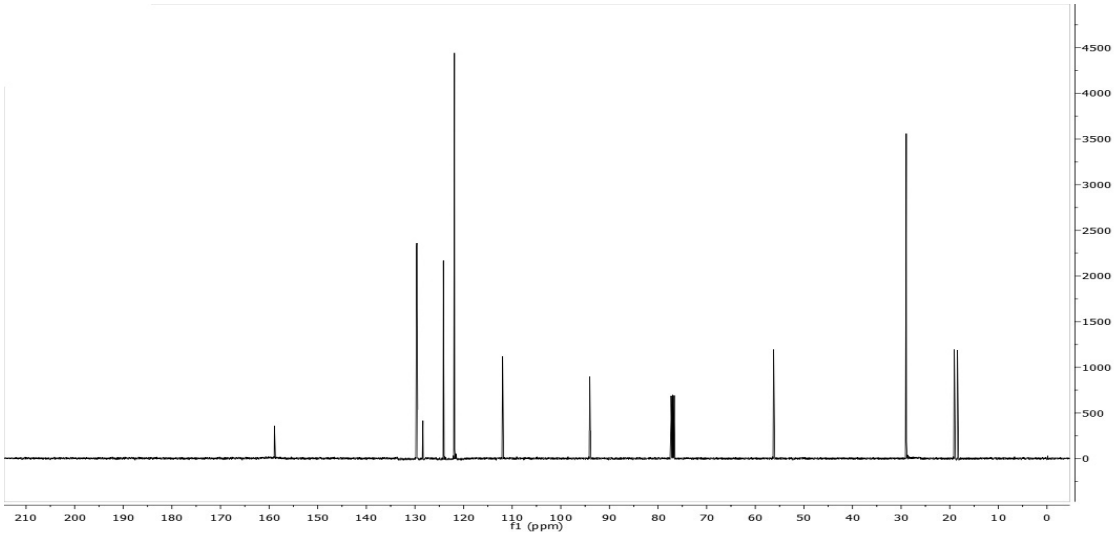




45c

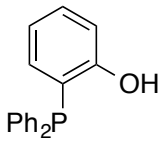
Methoxymethyl *o*-diisopropylphosphinophenyl ether 45c. 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.13 (4H, m), 5.97 (2H, s), 3.41 (3H, s), 1.65 (2H, m), 0.92 (12H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 129.8, 128.8, 124.3, 121.0, 111.0, 94.3, 55.8, 29.8, 18.5, 18.4.





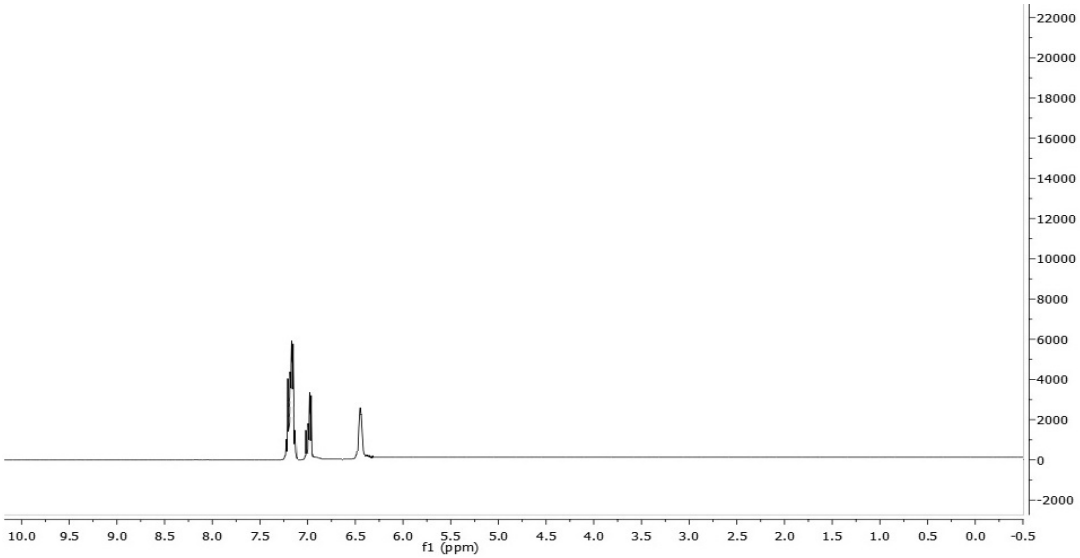
General Procedure for Synthesis of *o*-dialkylphosphinophenol 46.

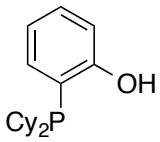
A solution of 4N HCl in diethyl ether was added to 5 mL of dry methanol. Methoxy-methyl *o*-dialkylphosphinophenyl ether (1 g, 3.1 mmol, 1 eq) was added at room temperature and under argon. The resulting solution was stirred for 1 h then the solvent was removed under reduced pressure giving a yellow oil. The residue was dissolved in dry MeOH (3 mL), then water was added until the cloud point was reached. The solution was stirred under argon while cooling, and the resulting white solid was filtered.



46a

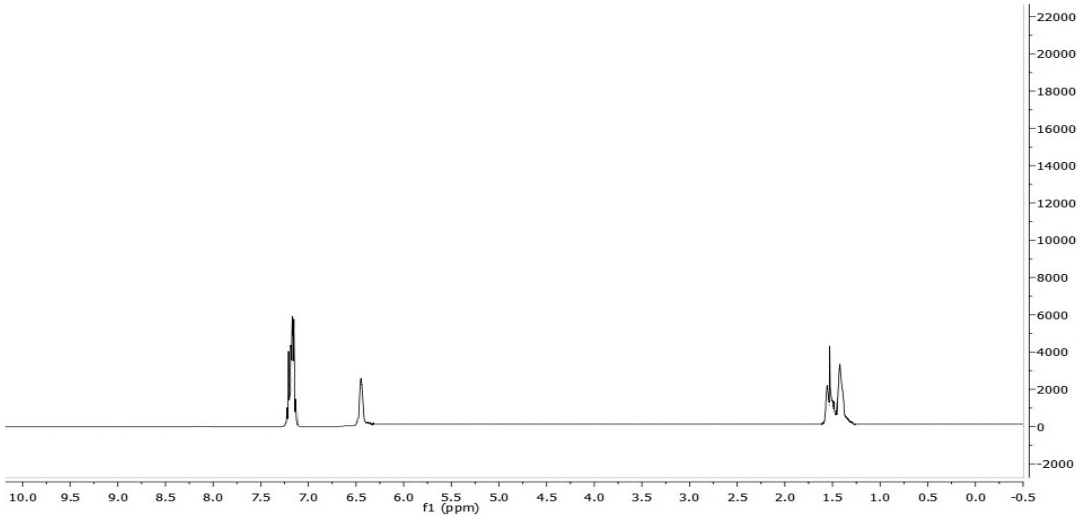
***o*-Diphenylphosphinophenol 46a.** 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.26 (11H, m), 7.05-6.86 (3H, m), 6.42 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 134.5, 134.4, 133.7, 133.6, 130.1, 128.8 (2 peaks), 128.7 (2 peaks), 121.6, 115.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ -26.6.

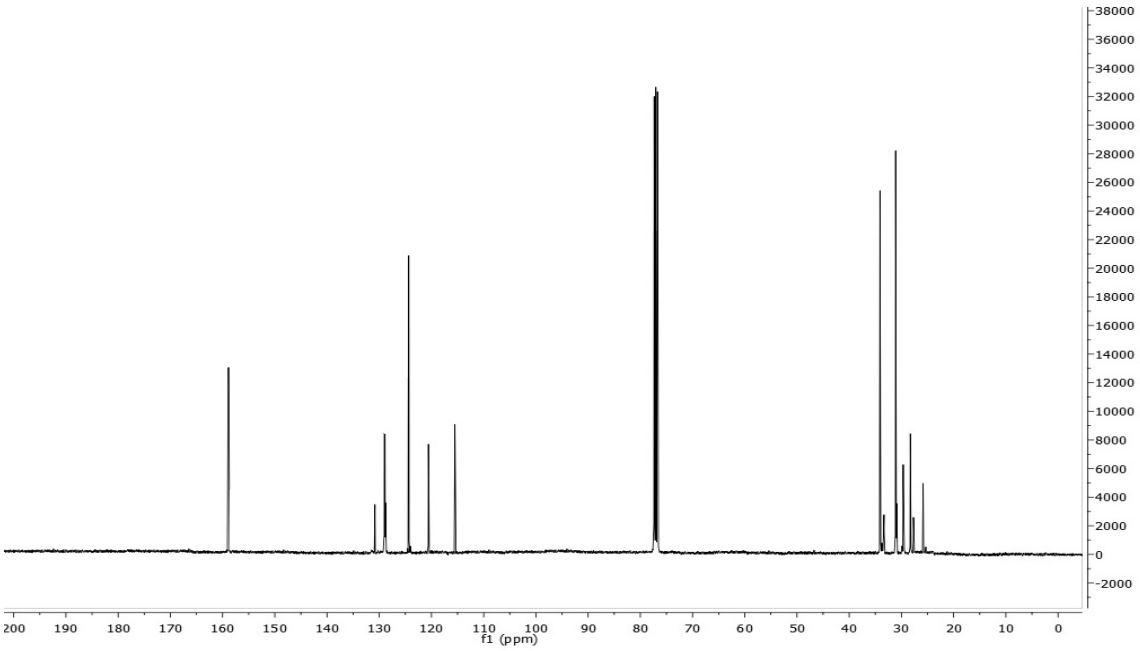


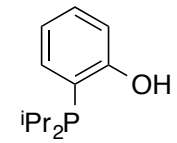


46b

***o*-Dicyclohexylphosphinophenol 46b.** 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.10 (4H, m), 6.42 (1H, br), 1.55-1.40 (22H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 130.2, 129.1, 125.8, 120.9, 115.3, 34.5, 34.3, 30.4, 28.9, 26.1.

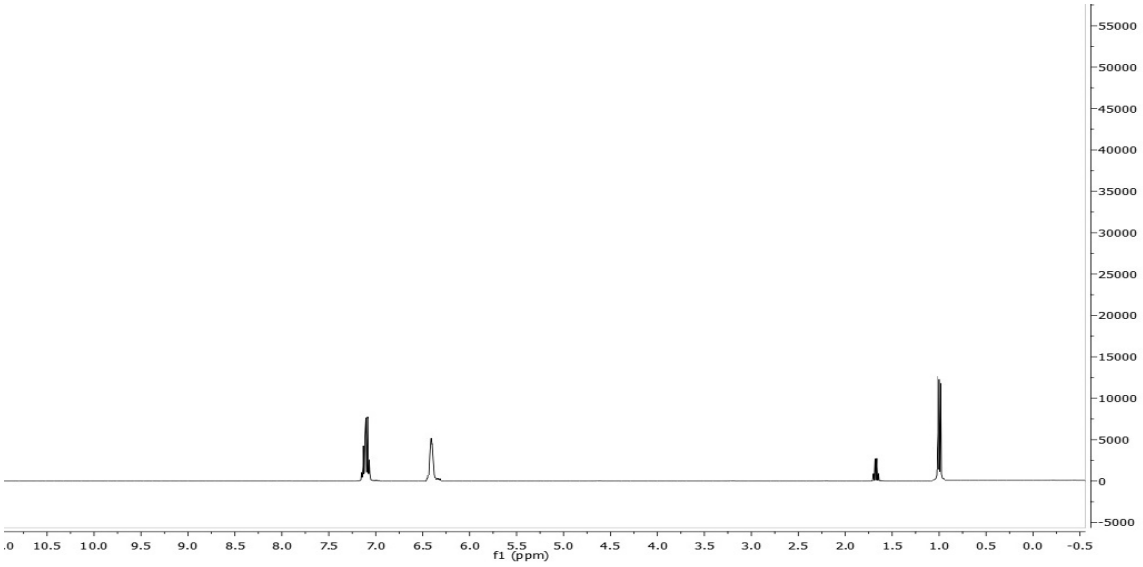


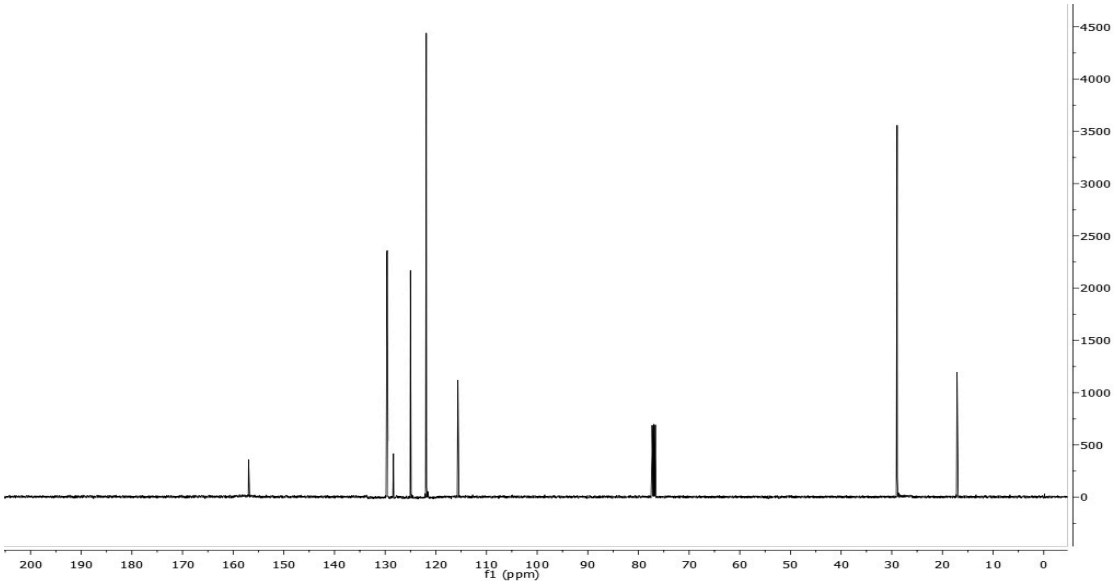




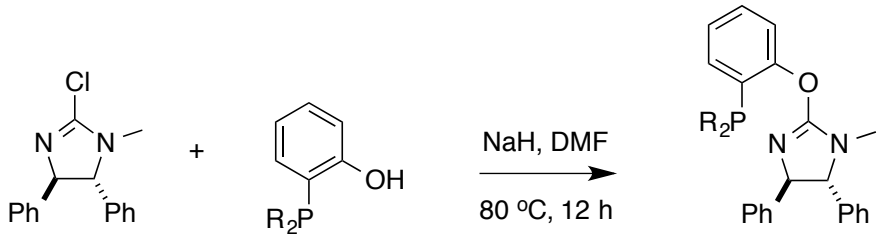
46c

***o*-Diisopropylphosphinophenol 46c.** 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-6.95 (4H, m), 6.42 (1H, br), 1.60 (2H, m), 0.93 (12H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.2, 129.2, 125.7, 120.9, 115.3, 29.9, 18.8.


55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

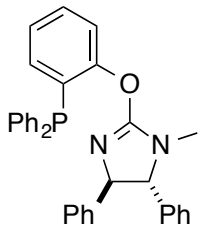

4500
4000
3500
3000
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

General Procedure for Preparation of (4*R*,5*R*)-2-(2-(Dialkylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole 47.



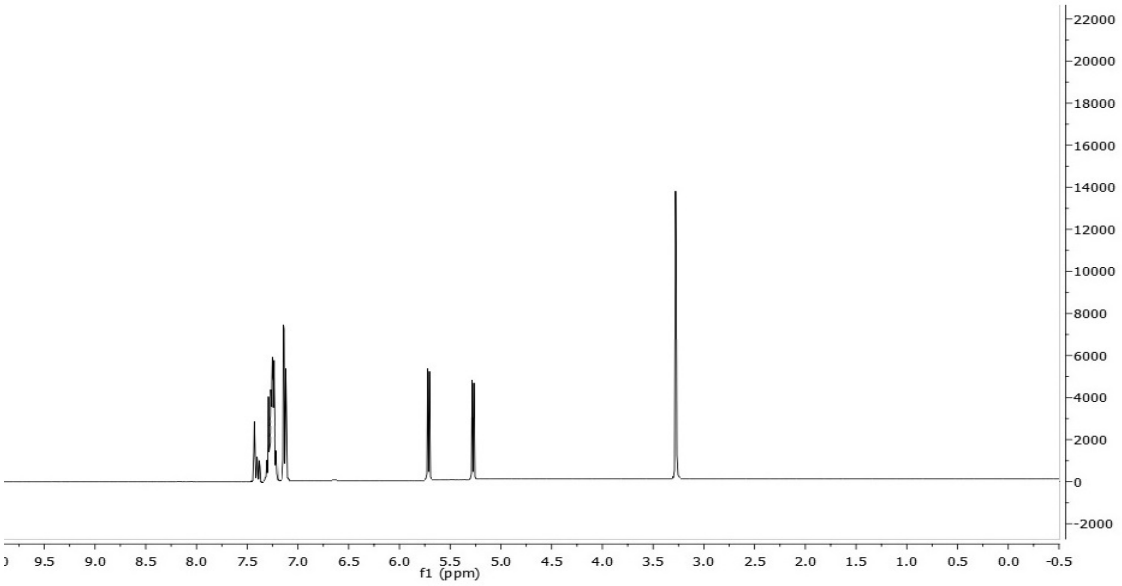
47

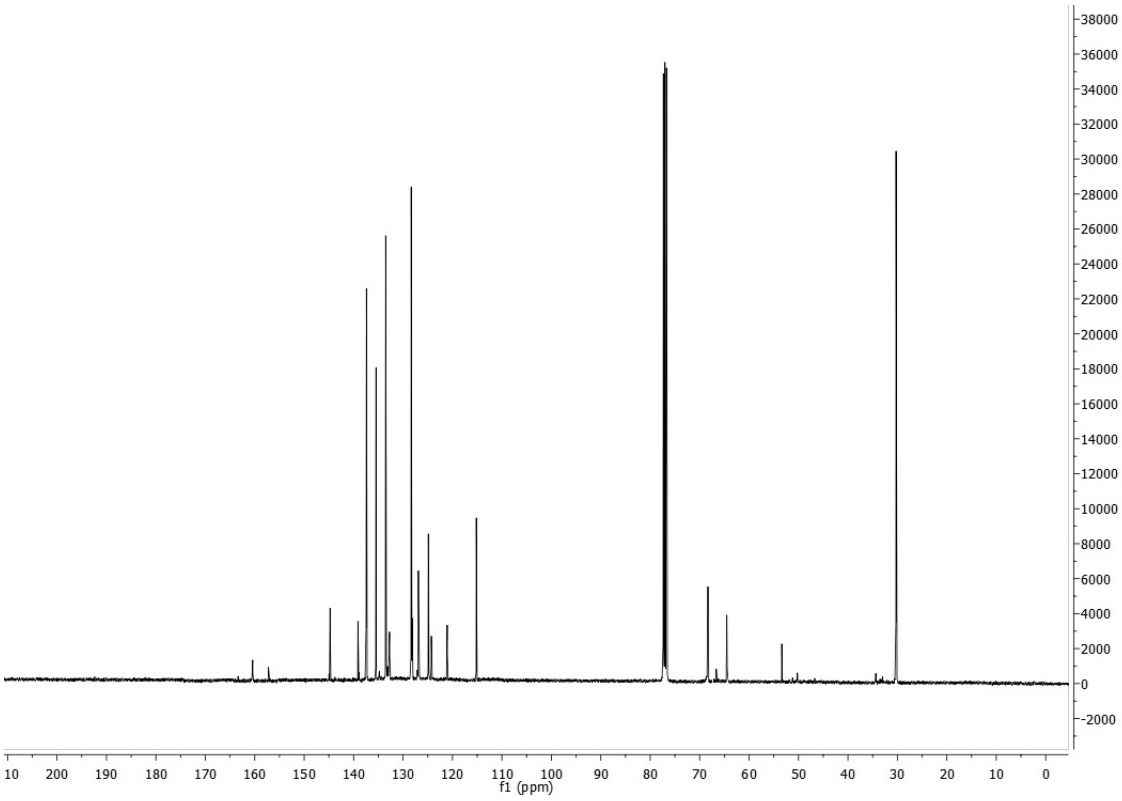
NaH was added to a stirred solution of *o*-dialkylphosphinophenol (1 mmol, 1 eq) in DMF 10 mL at 0 °C. The solution was allowed to warmed to room temperature and stirred for 2 h, then solution of (4*R*,5*R*)-2-chloro-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole (1 eq) in DMF was added. The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was cooled to room temperature, poured into ice-cold water, and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4. Solvent was removed under reduced pressure to provide the crude material as a yellow solid. Recrystallization from ethyl acetate/hexane afforded the desired product as a white solid.

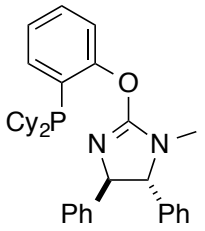


47a

(4*R*,5*R*)-2-(2-(Diphenylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole 47a. 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.11 (17H, m), 7.02-6.83 (7H, m), 5.73 (1H, d, *J* = 6.9 Hz), 5.25 (1H, d, *J* = 6.9 Hz), 3.21 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 157.8, 138.2, 137.2, 134.5, 133.7, 133.6, 128.7, 128.6, 128.4, 128.0, 127.0, 125.9, 121.3, 115.8, 67.9, 65.8, 30.1.

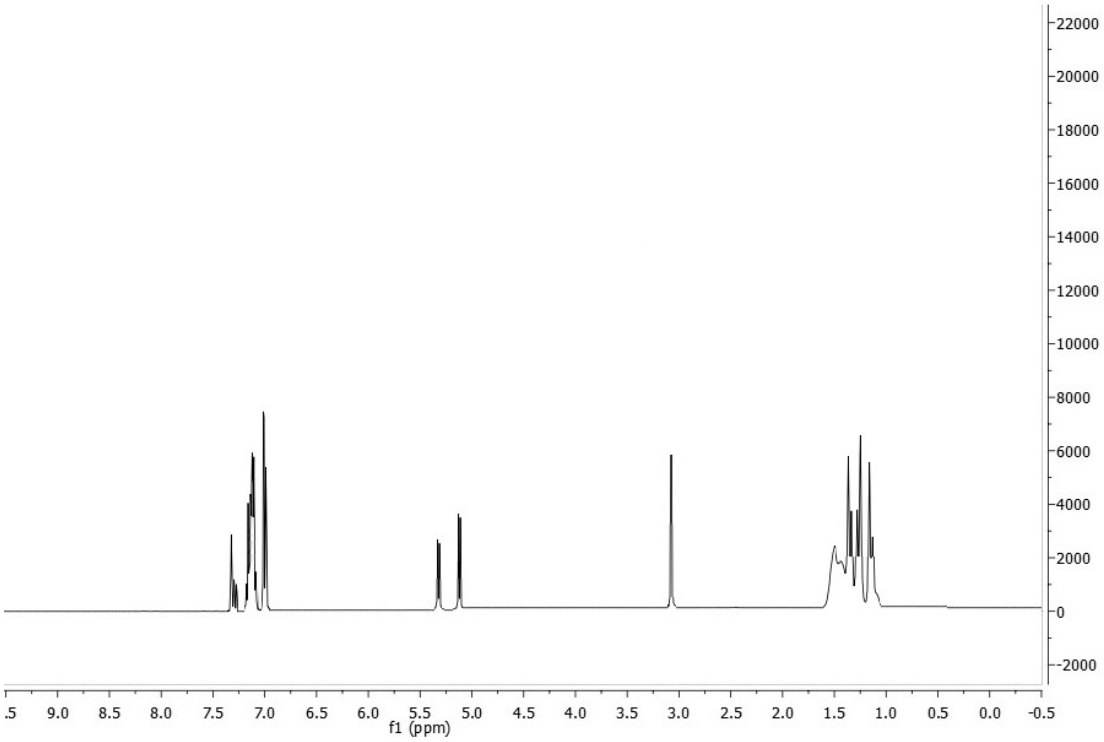

22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

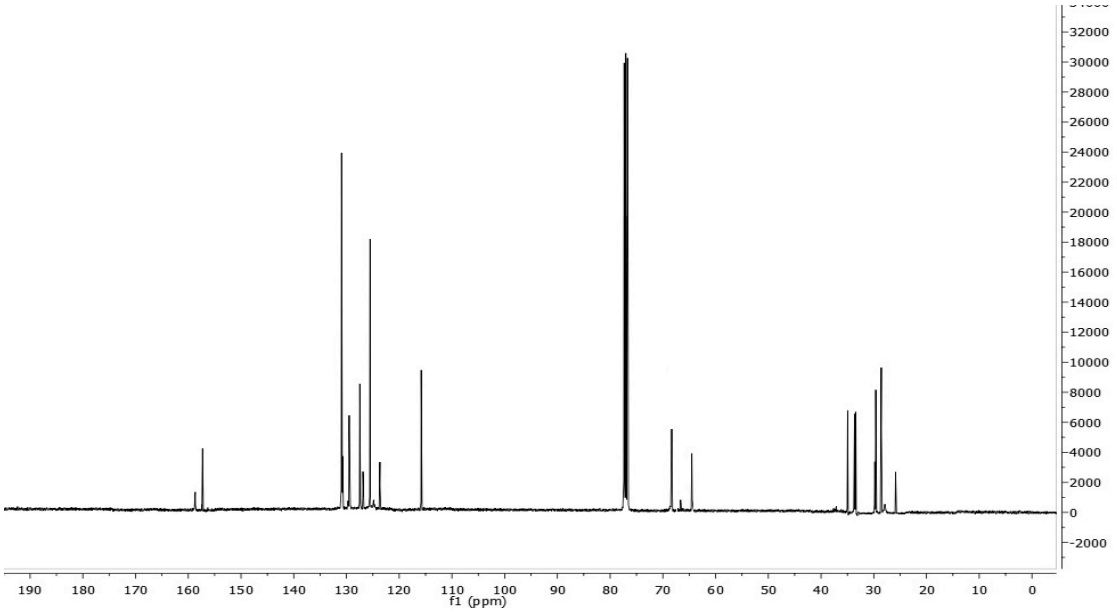

38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

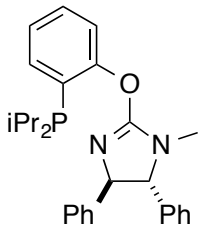


47b

(4*R*,5*R*)-2-(2-(Dicyclohexylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole 47b. 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.02 (14H, m), 5.65 (1H, d, *J* = 6.6 Hz), 5.28 (1H, d, *J* = 6.6 Hz), 3.05 (3H, s), 1.63-1.40 (22H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.6, 130.1, 129.2, 128.6, 128.5, 127.3, 127.0, 125.9, 125.6, 120.8, 115.3, 67.5, 61.3, 34.3, 34.1, 30.3, 29.1, 28.9, 26.0.

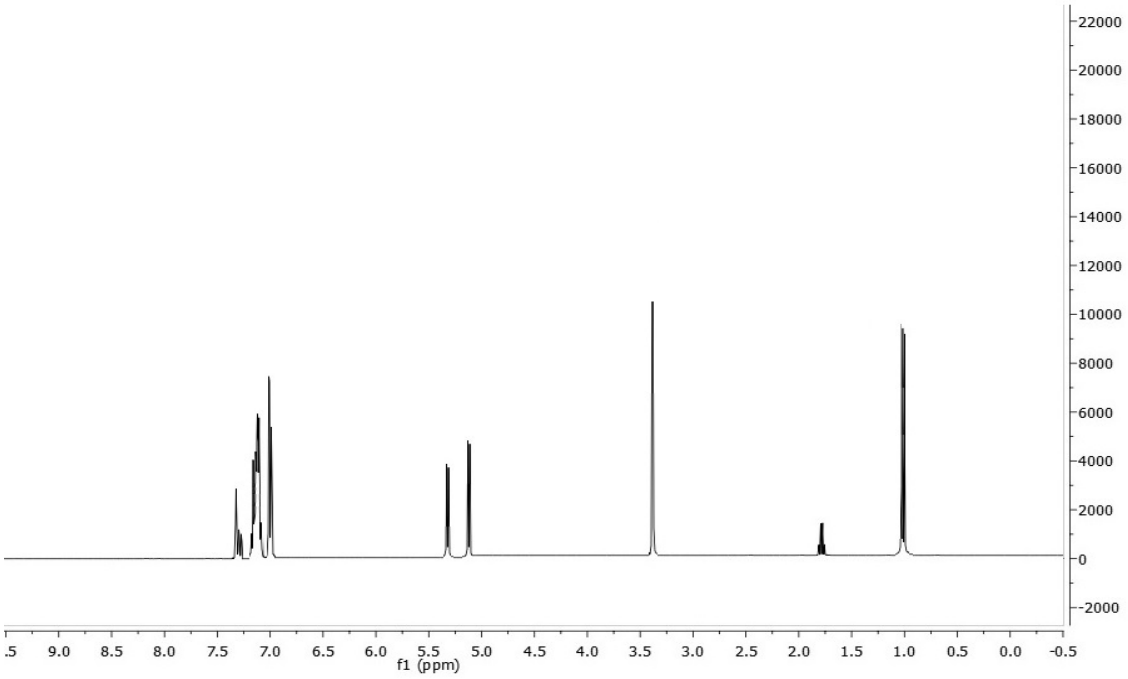


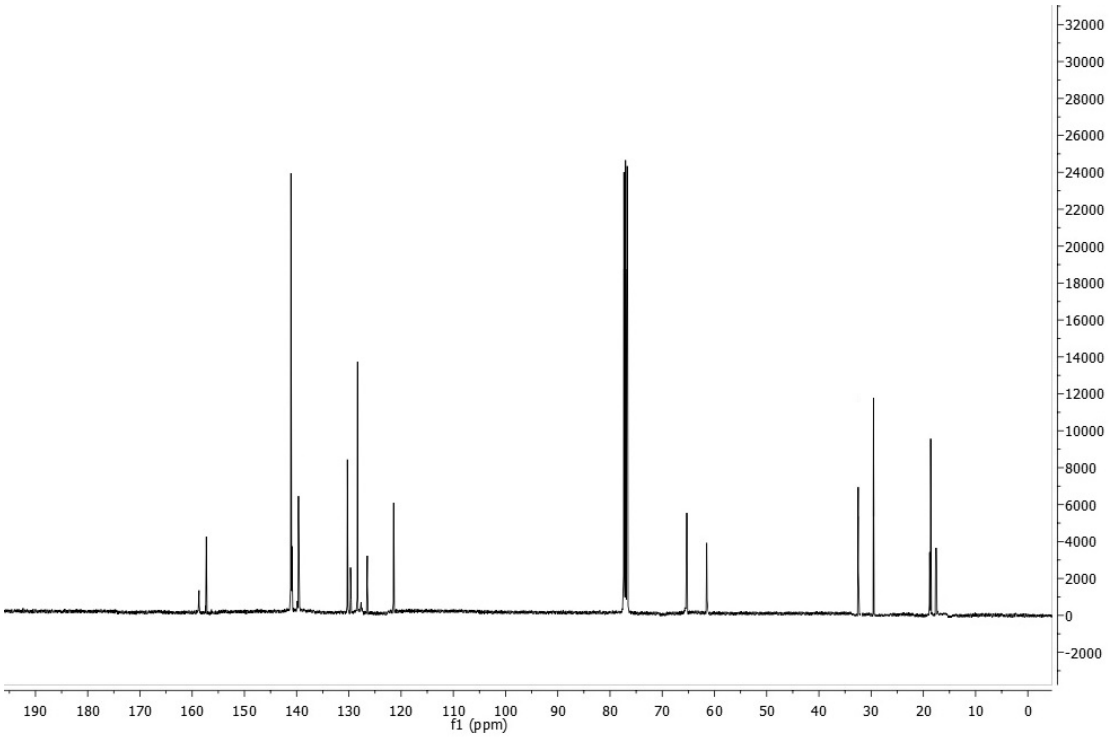




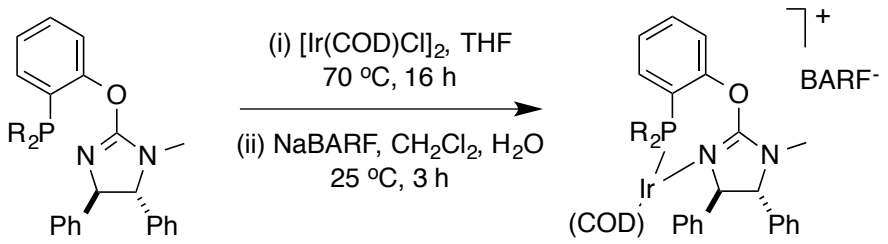
47c

(4*R*,5*R*)-2-(2-(Diisopropylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole 47c. 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-6.95 (14H, m), 5.33 (1H, d, *J* = 6.3 Hz), 5.12 (1H, d, *J* = 6.3 Hz), 3.44 (3H, s), 1.59 (2H, m), 0.95 (12H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.8, 140.3, 138.3, 130.1, 129.0, 128.6 (2 peaks), 128.4, 127.9, 127.7, 125.8, 120.1, 64.6, 61.6, 32.2, 29.9, 18.5.


22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

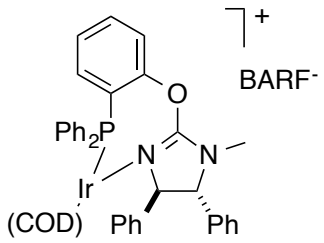

32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

General Procedure for Preparation of Iridium Catalyst 40.



47 **40**

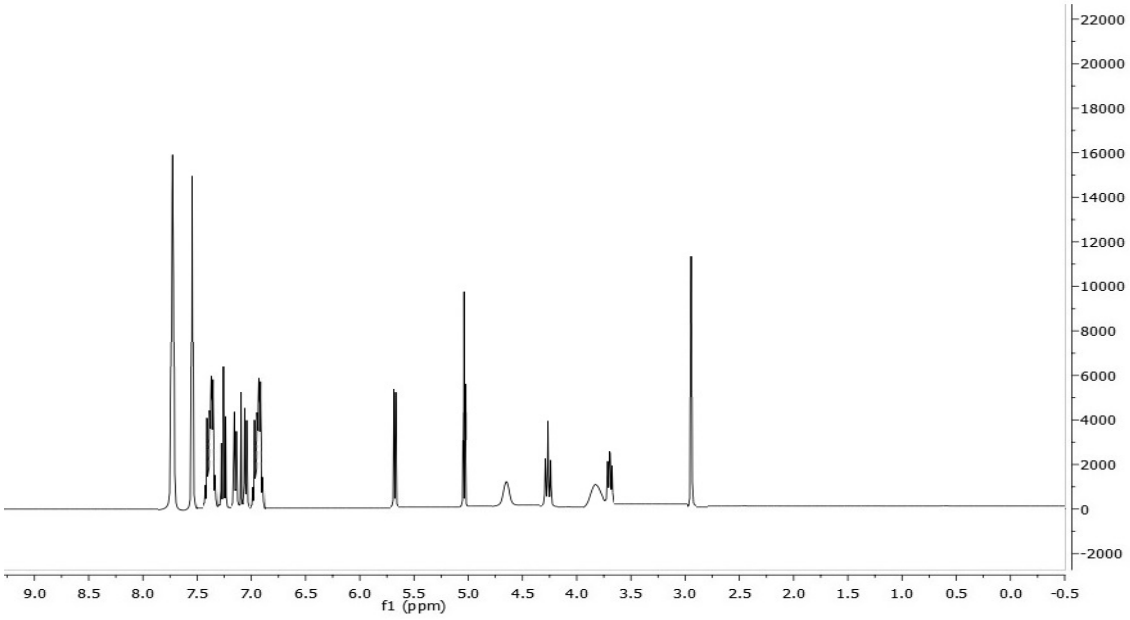
(4*R*,5*R*)-2-(2-(Dialkylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole **47** was added to a round bottom flask along with 0.5 equivalents of $[Ir(COD)Cl]_2$ under Ar. THF was syringed in to make the solution 0.03 M in imidazolium salt. The mixture was heated to 70 ^{o}C in an oil bath and stirred for 16 h. After cooling to room temperature, the volatiles were removed under reduced pressure and 1.5 equivalents of NaBARF in 5 mL CH_2Cl_2 was added. Water (5 mL) was added and the mixture was stirred vigorously for 15 min. The organic layer was removed and the aqueous layer was washed with an additional 5 mL CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4) and the volatiles were removed in *vacuo*. The residue was chromatographed using a short silica column and 10 % hexanes/CH_2Cl_2 as the eluent.

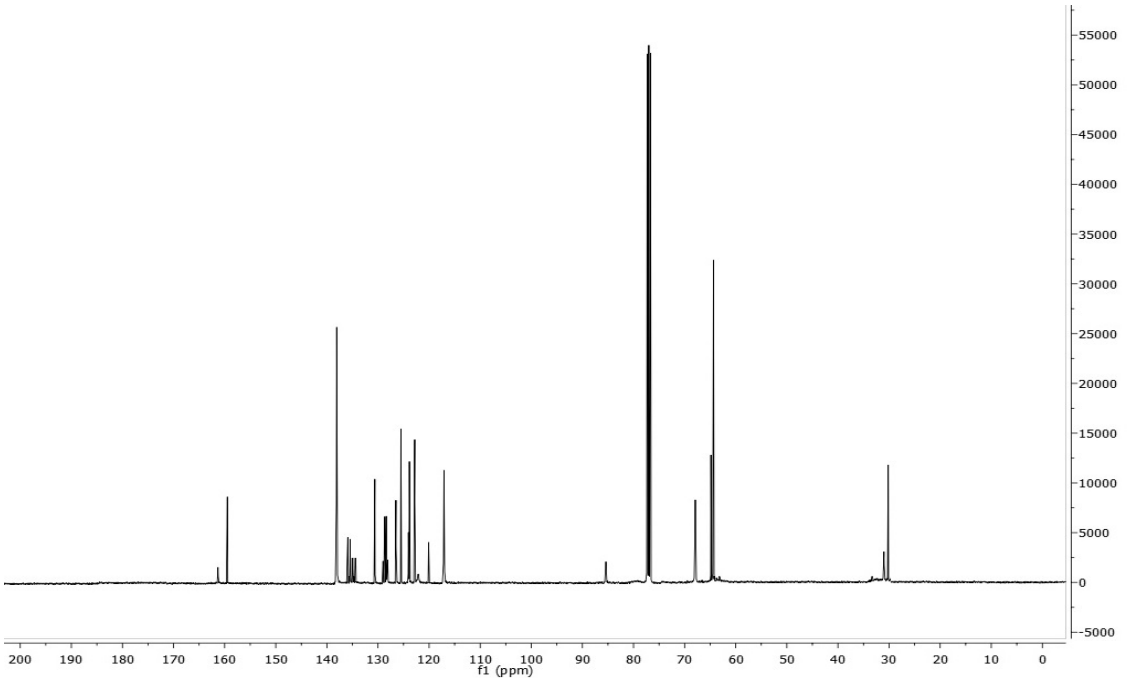


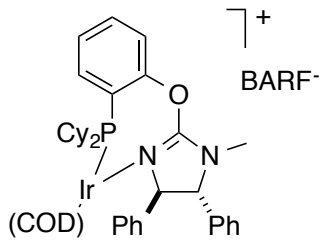
40a

(η^4-1,5-Cyclooctadiene)[(4*R*,5*R*)-2-(2-(Diphenylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole]iridium(I) Tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate 40a. (32 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (8H, s), 7.56 (4H, s), 7.41-7.12 (16H, m), 7.05-6.85 (8H, m), 5.73 (1H, d, *J* = 6.0 Hz), 5.13 (1H, d, *J* = 6.0 Hz), 4.74-4.60 (2H, m), 4.16-4.12 (2H, m), 3.97-3.58 (8H, m), 2.98 (3H, s); ^{13}C NMR (100

MHz, $CDCl_3$) δ 160.2, 158.8, 138.0, 137.5, 136.3, 134,9, 134.8, 134.5, 133.7, 133.6 (2 peaks), 128.7 (2 peaks), 128.6, 128.4 (2 peaks), 128.0, 127.0, 124.8, 122.7, 125.9, 121.3, 115.8, 85.5, 67.5, 66.3, 30.4.

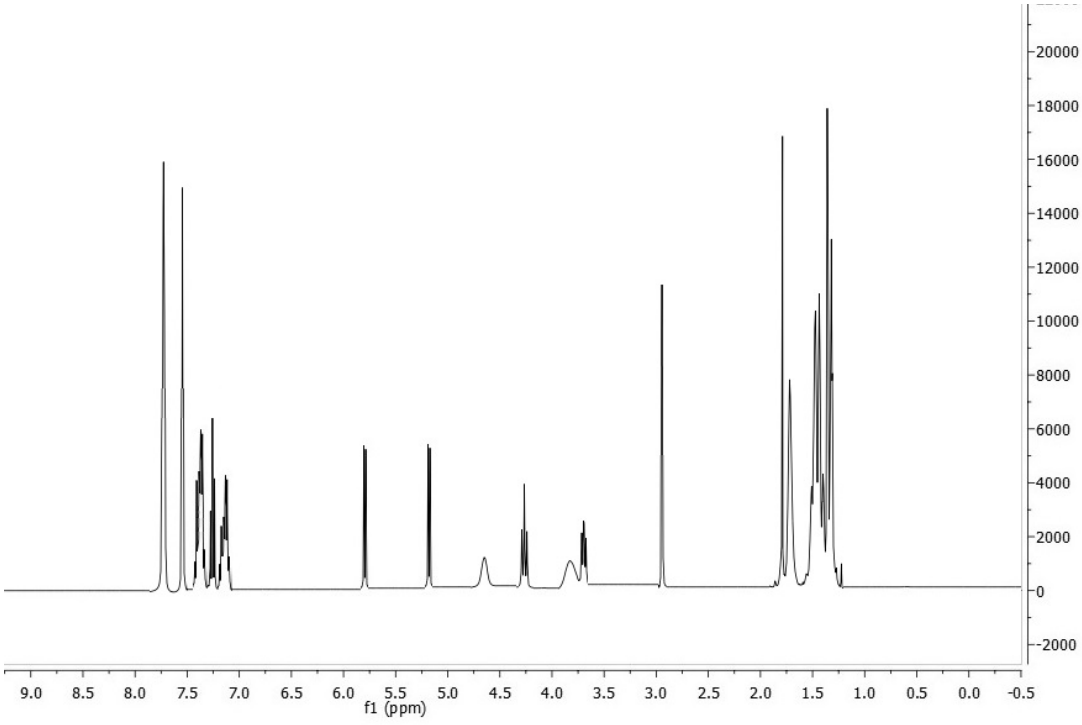


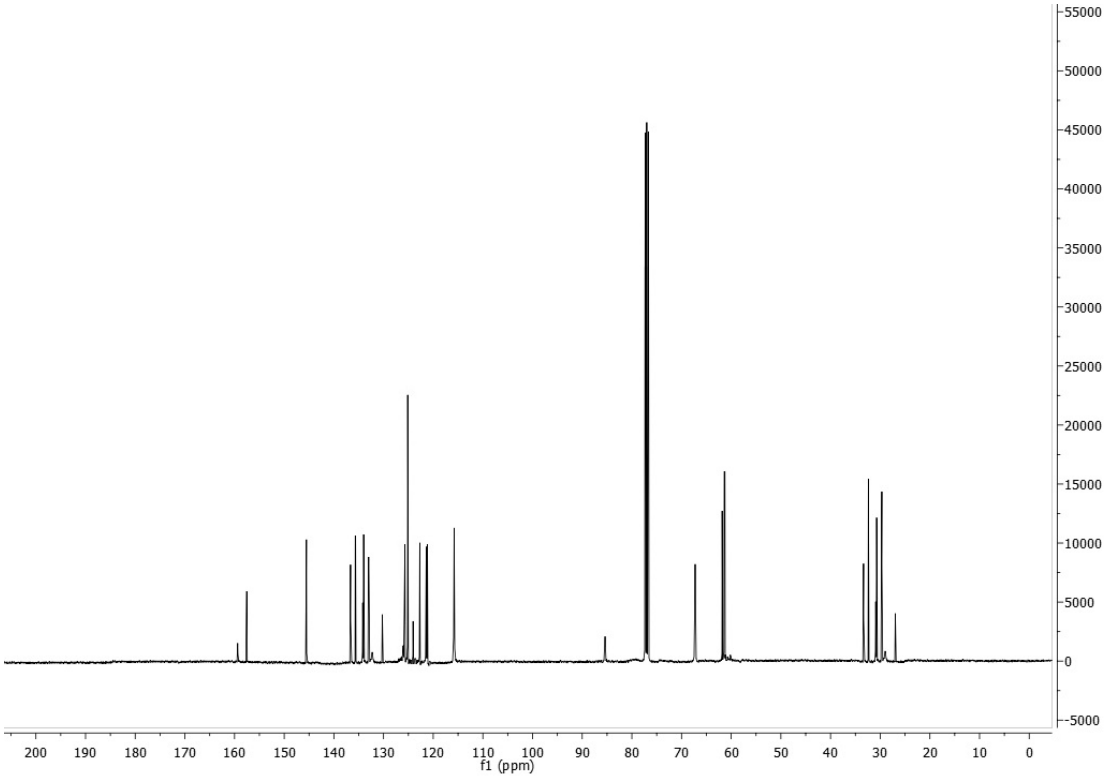


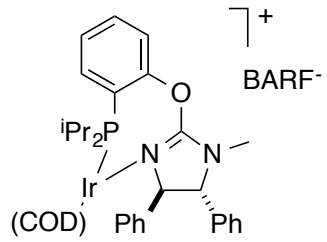


40b

(η^4-1,5-Cyclooctadiene)[(4*R*,5*R*)-2-(2-(Dicyclohexylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole]iridium(I) Tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate 40b. (27 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (8H, s), 7.57 (4H, s), 7.44-7.05 (14H, m), 5.84 (1H, d, *J* = 6.0 Hz), 5.25 (1H, d, *J* = 6.0 Hz), 4.70-4.63 (2H, m), 4.41-4.29 (2H, m), 4.01-3.59 (8H, m), 2.95 (3H, s), 1.75-1.33 (22H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 157.8, 146.7, 136.3, 134,9, 130.5, 129.5, 129.2, 129.1, 128.7 (2 peaks), 128.6, 128.5, 127.3, 127.0, 120.8, 115.5, 67.6, 61.0, 39.3, 34.3, 34.1, 30.3, 29.1, 28.6, 26.2.

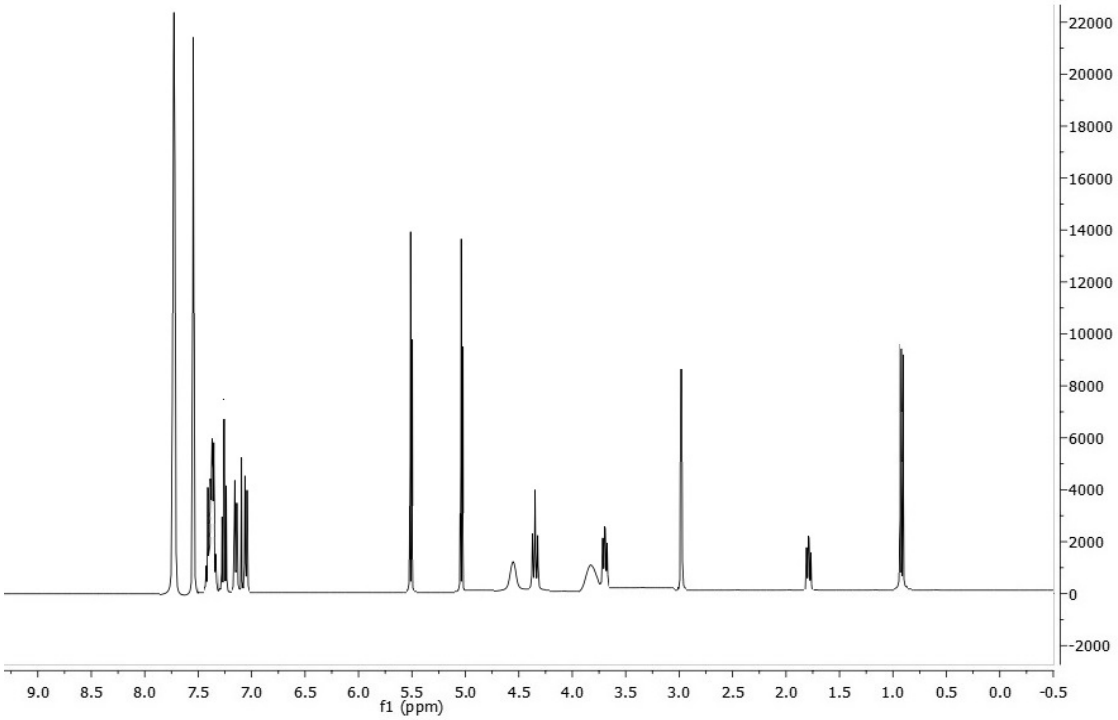


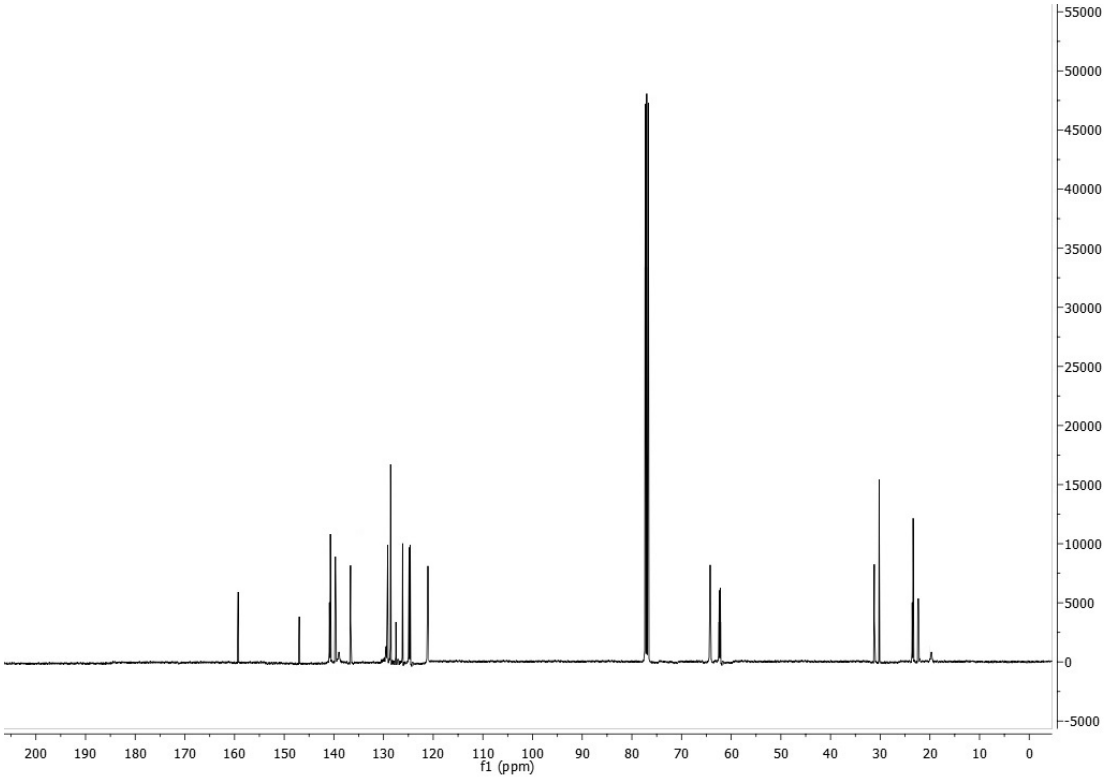




40c

(η^4-1,5-Cyclooctadiene)[(4*R*,5*R*)-2-(2-(Diisopropylphosphino)phenoxy)-1-methyl-4,5-diphenyl-4,5-dihydro-imidazole]iridium(I) Tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate 40c. (45 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (8H, s), 7.57 (4H, s), 7.44-7.05 (14H, m), 5.56 (1H, d, *J* = 6.0 Hz), 5.11 (1H, d, *J* = 6.0 Hz), 4.66-4.56 (2H, m), 4.41-4.32 (2H, m), 3.88-3.56 (6H, m), 1.65 (2H, m), 0.92 (12H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 146.7, 140.3, 138.3, 136.3, 134,9, 130.0, 129.0, 128.6, 128.7, 128.4, 127.9, 127.7, 125.8, 120.1, 64.6, 62.1, 61.6, 31.5, 28.8, 23.9, 22.9, 18.3.


22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

B. Catalytic Hydrogenation Conditions

The corresponding alkenes (0.1 mmol) and **40** (1 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.